Development of magnitude and number representation and its relation to space in typically developing children and children with developmental dyscalculia

Thesis (cumulative thesis)

Presented to the Faculty of Arts and Social Sciences

of the University of Zurich

for the Degree of Doctor of Philosophy

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Accepted in the Spring Term 2015

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Zurich, 2016

To my husband and our unborn child

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Acknowledgments

I would like to thank PD Dr Ruth O’Gorman Tuura and the MR-Team at the University Children's Hospital for giving me the possibility to do my PhD and for the support in the last years. My special thanks go to Prof Michael von Aster and Dr Karin Kucian for the financial and scientific support and for always encouraging me in my work. I am deeply grateful that I was given the opportunity to implement my own ideas and opinions in the present work. Last but not least I would like to thank you, Karin, for your friendship and the fun moments in the office that coloured the everyday working life. I am also grateful that I could share troubles, perks and hassles of a PhD with my team. My colleagues were always helpful and put a lot of effort into improvements for the whole MR-Centre. Thank you!

Further I would like to thank my PhD committee Prof Urs Maurer, Prof Lutz Jäncke and Prof Ernst Martin. Urs Maurer was exceptionally generous in supervising me, which I never took for granted in the university environment.

I owe enormous thanks to my parents and my brother, without whom I could not have reached my goals. Eu sun enorm grata per voss sustegn finanzial dürant mia educaziun all’università. Grazia a vus n’haja eu survendschì ils temps difficils in mia vita e sun dvantada la persuna ch’eu sun. I would also like to thank my friends for filling my life with so much more than academic content. It means a lot to me knowing you in my life. Most of all, I am deeply grateful to my husband Michael for his unconditional love and support. Thank you for giving me the biggest gift life offers!

Abstract

Numbers and mathematics are a substantial part of our culture and society considerably influencing our decisions on a daily base. Poor numeracy poses a serious burden for persons affected and makes it difficult to function effectively in our everyday's life. The innate ability to process numerosities usually enables us to develop complex mathematical skills at a young age. However, children with developmental dyscalculia struggle with the acquisition of numerical and arithmetical skills. Despite the high prevalence of 3-7% and the importance of being numerate in society, development dyscalculia remains a neglected problem. Hence, little is known about the neuronal development of numerical cognition.

The aim of the present thesis is to gain understanding about the development of numerical cognition in typically achieving children and, in particular, children with developmental dyscalculia. The intricate relationship of space and number was investigated considering the possibility of a generalised magnitude system. Longitudinal functional magnetic resonance imaging and behavioural data were acquired in order to trace typical and atypical developmental effects.

Results of the longitudinal study reveal that in typical development numerical representations specialise with age and experience, resulting in a consistent and well-developed fronto-parietal network. In contrast, persistent deficits in number processing and arithmetical skills are found in children with developmental dyscalculia compared to their peers. Brain imaging results suggest an age-related activation increase in number-specific regions pointing to a promising continuation in neuronal development in dyscalculic subjects. However, the increase in domain-general regions and the progression to a rather diffuse instead of a focussed number network corroborates the view of a delayed and inefficient developmental course.

The results of the second study show that continuous and discrete magnitudes were both processed with high accuracy and almost identical neuronal networks. This favours the view that continuous and discrete magnitudes might rely on one generalised system for magnitude. Moreover, the ability to process continuous and discrete magnitudes is specialised in typically developing

adolescents and seems to be preserved in subjects with developmental dyscalculia. Neuronal findings also point to the use of compensatory systems, suggesting a slight delay in the development of the discrete and continuous numerical system in developmental dyscalculia.

The present data is only a first attempt to understand the typical and atypical developmental course of numerical cognition. Future studies need to put effort in the understanding of the complex dependencies and interconnections of the single factors in developmental dyscalculia leading to effective and practical implications for education and therapy.

Zusammenfassung

Zahlen und Mathematik sind ein substantieller Bestandteil unserer Gesellschaft und Kultur und beeinflussen unsere alltäglichen Entscheidungen. Verminderte Zahlen- und Rechenkenntnisse stellen eine grosse Belastung für die betroffenen Personen dar und erschweren die Funktionsfähigkeit im alltäglichen Leben beachtlich. Die angeborene Fähigkeit, Mengen zu verarbeiten, ermöglicht bereits relativ früh komplexe mathematische Fähigkeiten zu erwerben. Kinder mit entwicklungsbedingter Dyskalkulie zeigen hingegen Schwierigkeiten beim Erwerb numerischer und arithmetischer Fähigkeiten. Trotz der hohen Prävalenz von 3-7% und der Wichtigkeit intakter Zahlen- und Rechenkenntnissen in der Gesellschaft erfährt Dyskalkulie wenig Beachtung. Folglich ist das Wissen über die neuronale Entwicklung numerischer Kognition heute noch unzureichend.

Ziel der vorliegenden These ist es, Erkenntnisse über die Entwicklung numerischer Kognition bei typisch entwickelnden Kindern und besonders Kindern mit Dyskalkulie zu erlangen. Unter der Annahme eines generellen Grössenverarbeitungssystems wurde die komplexe Relation von Raum und Zahlen untersucht. Des Weiteren wurden longitudinale funktionelle Magnetresonanz Tomographie- und Verhaltensdaten erhoben, um typische und atypische Entwicklungseffekte zu messen.

Die Resultate der Langzeitstudie zeigen, dass während der typischen Entwicklung eine Spezialisierung der numerischen Repräsentation mit zunehmendem Alter und Erfahrung stattfindet. Dies resultiert über die Zeit in einem konsistenten und gut entwickelten fronto-parietalen Netzwerk. Demgegenüber finden sich bei Kindern mit Dyskalkulie persistente Defizite in der Zahlenverarbeitung und in den arithmetischen Fähigkeiten. Die funktionellen Ergebnisse decken eine altersabhängige Aktivierungszunahme in zahlenspezifischen Regionen auf, was auf eine vielversprechende Kontinuität in der neuronalen Entwicklung von dyskalkulischen Kindern hinweist. Die Aktivitätszunahme in domänen-übergreifenden Regionen und die Entwicklung zu

einem eher diffusen anstatt fokussiertem Zahlennetzwerk, bekräftigen jedoch die Ansicht eines verzögerten und ineffizienten Entwicklungsverlaufes.

In der zweiten Studie konnte gezeigt werden, dass kontinuierliche und diskontinuierliche Grössen akkurat und von einem beinah identischen neuronalen Netzwerk verarbeitet werden. Dies unterstützt die Annahme, dass beiden ein generelles System für Grössenverarbeitung zugrunde liegt. Zudem ist die Verarbeitung kontinuierlicher und diskontinuierlicher Grössen in typisch entwickelnden Adoleszenten hoch spezialisiert und scheint bei Probanden mit Dyskalkulie erhalten zu sein. Die neuronalen Ergebnisse lassen jedoch die Nutzung von Kompensationsmechanismen vermuten, was auf eine leichte Verzögerung in der Entwicklung des kontinuierlichen und diskontinuierlichen numerischen Systems bei Jugendlichen mit Dyskalkulie hinweist.

Die vorliegenden Resultate sind lediglich eine erste Bestrebung, um Erkenntnisse über den typischen und atypischen Entwicklungsverlauf numerischer Kognition zu erlangen. Zukünftige Studien sollten die komplexen Abhängigkeiten und Zusammenhänge der einzelnen Faktoren in Dyskalkulie adressieren, um effektive und praktische Implikationen für Bildung und Therapie formulieren zu können.

Abbreviations

DD	developmental dyscalculia,
TD	typically developing
ANS	approximate number system
ATOM	a theory of magnitude
SNARC	spatial numerical association of response codes
AG	angular gyrus
IFG	inferior frontal gyrus
IOG	inferior occipital gyrus
IPL	inferior parietal lobe
IPS	intraparietal sulcus
MFG	middle frontal gyrus
MOG	middle occipital gyrus
MTG	middle temporal gyrus
PHG	parahippocampal gyrus
SFG	superior frontal gyrus
SMG	supramarginal gyrus
SMdG	superior medial gyrus
SPL	superior parietal lobe

1 Introduction

Numbers are omnipresent in our lives and its importance for the society has been underestimated for a long time. Recently conducted studies about long term consequences and societal costs of innumeracy (Gross, 2009; Parsons & Bynner, 2005) underpin the importance to understand more about numerical cognition. Intensified research efforts on numerical cognition and innumeracy over the last years have led to more scientific publications and public awareness. Acknowledging this development, the United Kingdom, for instance, has launched a national numeracy campaign (http://www.nationalnumeracy.org.uk). Nevertheless, the number of publications and the funding for developmental dyscalculia is substantially lower than in developmental dyslexia despite having similar prevalence rates (Bishop, 2010). Furthermore, little is known about the typical and atypical brain development of numerical abilities. More insights from this field could contribute to the implementation of interventions and therapy for children with difficulties in mathematics.

The aim of the herewith presented thesis is to better understand the development of numerical cognition in typically developing children and in children with developmental dyscalculia by means of longitudinal behavioural and brain imaging data. In this regard, the special relationship of space and magnitude is investigated in consideration of the proposed general magnitude system (A Theory Of Magnitude, ATOM) (Walsh, 2003).

In a first part, the development of numerical cognition and the characteristics of developmental dyscalculia are introduced. After emphasizing the importance of studying development and presenting the used methods, two empirical studies are discussed in detail.

1.1 Development of numerical cognition

1.1.1 Infant capacities of number processing

It is widely recognised that non-verbal infants are able to process numerosities. This ability most probably goes back to an evolutionary ancient numerical system that is also found in studies with animals and across various species (e.g. monkeys, fish, birds) (e.g. Agrillo, Piffer, & Bisazza, 2011; Brannon & Terrace, 1998; Rugani, Fontanari, Simoni, Regolin, & Vallortigara, 2009). Research of the last three decades impressively demonstrates that infants are capable from the first day after birth to discriminate small and big quantities visually and auditorily (Izard, Sann, Spelke, & Streri, 2009; Starkey, Spelke, & Gelman, 1990; Xu, Spelke, & Goddard, 2005); for an overview see Cantrell and Smith (2013). The performance in this 'approximate number system' (ANS) depends on the ratio of the presented numerosities, which increases during development reflecting a refined number acuity over time (Brannon, Lutz, & Cordes, 2006; Brannon, Suanda, & Libertus, 2007). Moreover it has been suggested that small numerosities up to three items (in adults up to five) are processed in a precise and simultaneous manner (subitizing) (Mandler & Shebo, 1982; Xu et al., 2005). It is however controversially discussed whether numerosities in the subizing range are processed by the ANS or by a separate system. Neuroimaging studies provide further evidence for that question. Using near infrared spectroscopy (NIRS), Hyde et al. (2010) were able to show that 6-month-old infants already have a right parietal specialisation for numbers. In a further study, small (subitizing) and large numerosities evoked distinct responses regarding localisation and time of the event-related potential (ERP) (Hyde & Spelke, 2012). This indicates that infants already have two separate and specialised systems to process numerosities.

1.1.2 The role of number words

Soon after learning to speak children are confronted with number and quantity related words (e.g. two, three, more, less). Learning to count is an essential step in the development of numerical cognition and normally is accomplished in different stages (as described by Gelman &

Gallistel, 1978). Number words provide a system upon which the approximate numerosities can be mapped to precise quantities. This has been confirmed by studies with indigenous tribes of the Amazon forest having only limited number words in their languages. Subjects of the mentioned studies were well able to estimate numerosities and perform a task of exact numerical equivalence as long as the numerosity was visible (Frank, Everett, Fedorenko, & Gibson, 2008; Pica, Lemer, Izard, & Dehaene, 2004). Thus, number words seem to be particularly important when exact quantities have to be represented, stored and manipulated over time, space and modality (Frank et al., 2008).

1.1.3 Development of arithmetic competencies

The ability to represent, store and manipulate exact quantities is important for the acquisition of arithmetical competencies and higher mathematical skills. Initially children use finger counting strategies to obtain results for calculation problems. With increasing proficiency there is a shift from simple (counting all) to more sophisticated (counting on from larger) calculation strategies (Butterworth, 2005; Carpenter & Moser, 1982), eventually leading to arithmetical fact retrieval. On the neuronal level, the growing proficiency in fact retrieval has been related to an activation increase in the entire frontal-parietal numerical network and significantly greater functional connectivity between the prefrontal cortex and occipito-parietal areas (Cho, Ryali, Geary, & Menon, 2011; Rosenberg-Lee, Barth, & Menon, 2011).

1.1.4 Developmental changes in number representation

During development the initial capacity of processing approximate numerosities changes trough experience and education. The internal representation of number and quantity is reported to be spatially oriented and organised, also known as the mental number line (Berch, Foley, Hill, & Ryan, 1999; Dehaene, 2003). The formation of such a representation is assumed to begin at early age and refine during development (Ebersbach, Luwel, Frick, Onghena, & Verschaffel, 2008; Siegler & Booth, 2004; von Aster & Shalev, 2007). In a longitudinal study with children aged between 7 and 9 years, Landerl (2013) revealed that the efficiency to process numbers increased during development. By the age of 9 years children seem to connect Arabic numerals automatic with its magnitude representation (van Galen & Reitsma, 2008). It has further been shown, that linearity of the mental number line is correlated with arithmetical knowledge and predictive for learning unfamiliar arithmetical problems (Booth & Siegler, 2008).

These developmental changes can also be detected on the neuronal level. In a meta-analysis Kaufmann et al. (2011) investigated age-depended changes for non-symbolic number processing. Children seem to activate more anterior intraparietal regions, whereas the adults' activation is located more posterior. According to the authors, this is possibly due to a stronger use of finger based strategies in children (Kaufmann et al., 2008, 2011). Further evidence points to a developmental shift from a controlled and effortful frontal activation to an efficient number processing activation in the parietal cortex (Ansari, Garcia, Lucas, Hamon, & Dhital, 2005; Holloway & Ansari, 2010; Kucian, von Aster, Loenneker, Dietrich, & Martin, 2008; Rivera, Reiss, Eckert, & Menon, 2005). This effect was, however, not found in the meta-analysis of Kaufmann and colleagues (Kaufmann et al., 2011). Importantly, this shift was often reported in studies using symbolic number processing tasks and calculation problems and should therefore not be generalised to non-symbolic number processing. Emerson and Cantlon (2014) show in their study that during development the neuronal response to number related stimuli differs between the right and the left intraparietal sulcus. The right intraparietal sulcus exhibits stable and continuous activation present from early childhood on. The activation of the left intraparietal sulcus increases in dependence of learning exact numerical presentations. This is in line with the notion that the right intraparital sulcus is involved in the approximate numerical system and the left intraparietal sulcus develops its function with the growing acuity of numerical representation (Emerson & Cantlon, 2014; Hyde et al., 2010).

1.1.5 Developmental models of numerical cognition

The growing body of neuroimaging and neuropsychological research resulted in the formation of several models on numerical and mathematical cognition. One of the most influential models is the triple code model by Dehaene and Cohen (1995; see also Dehaene, Piazza, Pinel, & Cohen, 2003) predicting three different number representation in the brain: a quantity system located in the bilateral intraparietal sulcus supporting nonverbal quantity representation, a verbal system located in the left angular gyrus processing verbal aspects of numbers (e.g. fact retrieval), and a visual system located in the posterior superior parietal lobe involved in encoding Arabic numerals and spatial attention. Although the triple code model has found a lot of validation in behavioural and neuroimaging studies (e.g. Klein et al., 2014; Schmithorst & Brown, 2004) some important extensions have been proposed recently (Arsalidou & Taylor, 2011; Fias, Menon, & Szucs, 2013). Additional regions involved in attention (insula and prefrontal cortex), decoding number form (inferior temporal cortex), working memory and cognitive control (parietal, frontal, temporal and subcortical areas) have been identified and implemented into the model; for a more detailed description see the works by Arsalidou and Taylor (2011) and Fias, Menon and Szucs (2013).

The aforementioned models are arguably important for the understanding of numerical cognition but they do not necessarily contribute to the developmental perspective of the numerical brain (see also Kaufmann et al., 2011). Based on neuroimaging findings, von Aster and Shalev (2007) proposed a hierarchical four-step developmental model. The inherited core-system of magnitude representation builds the base for numerical cognition upon which number words and Arabic symbols are learned and associated with the corresponding magnitude. This further leads to the formation of a number line in which ordinality is built as a second core principle of numerical representation (von Aster & Shalev, 2007). A more recently formulated model suggested distinct components for number processing and calculation both falling back on a number representation which functionally specialises during development (Kaufmann et al., 2011; Kucian & Kaufmann, 2009). Additionally, the importance of cognitive and non-cognitive domain-general factors such as working memory, monitoring, and socio-emotional factors are thought to support the functioning and formation of numerical cognition (Kaufmann et al., 2011; von Aster & Shalev, 2007). In general, the work from the last decade acknowledges the need for developmental models rather than using adult models to explain numerical development. Furthermore, it has recognised the importance of domain general factors reflecting the interconnectivity of the brain and its functions.

1.2 Developmental dyscalculia

1.2.1 Definition and diagnosis of developmental dyscalculia

According to the International Classification of Diseases, 10th revision, (ICD-10, F81.2), developmental dyscalculia (DD) is a learning disability involving a specific impairment in the acquisition of numerical-arithmetical skills that is not solely explicable by general mental retardation or inadequate schooling (WHO, 2010). Furthermore, the diagnostic criteria of the ICD-10 (Clinical descriptions and diagnostic guidelines) demand that the arithmetical performance is significantly below the performance in general intelligence. This has been criticised in the literature over the last years, due to weak evidence for the existence of a IQ discrepancy criterion and practical limitations (Ehlert, Schroeders, & Fritz-Stratmann, 2012; von Aster, Schweiter, & Weinhold Zulauf, 2007). In fact, studies showed that mathematical performance does not differ between a dyscalculic group who meets the discrepancy criterion and a group that does not (Brankaer, Ghesquière, & De Smedt, 2014; Ehlert et al., 2012). As a consequence, the recently published Diagnostic and Statistical Manual of Mental Disorders, fifth edition, (DSM-5) adapted their diagnostic criteria to no longer requiring an IQ discrepancy (American Psychiatric Association, 2013). This change in the diagnostic criteria better accounts for the clinical profile of DD and is promising regarding the future direction of diagnostics.

1.2.2 Prevalence and comorbidity

Developmental dyscalculia occurs with a prevalence of 3-7% (Butterworth, Varma, & Laurillard, 2011; Gross-Tsur, Manor, & Shalev, 1996; von Aster et al., 2007; Wyschkon, Kohn, Ballaschk, & Esser, 2009) and has been shown to have a persisting character (Geary, Hoard, Nugent, & Bailey, 2013; Mazzocco, Murphy, Brown, Rinne, & Herold, 2013; Shalev, Manor, Auerbach, & Gross-Tsur, 1998; Shalev, Manor, & Gross-Tsur, 2005). Boys and girls seem to be affected equally, although some recent studies found a preponderance of girls (Fischbach et al., 2013; Gross-Tsur et al., 1996; Landerl & Moll, 2010).

Comorbide disorders, such as dyslexia and attention deficit and hyperactivity disorder (ADD/ADHD), are reported in 25-40% of the children with dyscalculia (Gross-Tsur et al., 1996; Landerl & Moll, 2010; von Aster & Shalev, 2007). Also secondary consequences resulting from failure and problems at school are found (e.g. Auerbach, Gross-Tsur, Manor, & Shalev, 2008). In addition, dyscalculic children often develop a negative attitude regarding numbers and mathematics, which can lead to math-specific anxiety. It has been shown that there is a direct link between emotions, arithmetic and low achievement, which in turn seems to reduce working memory capacity and activation in frontal areas involved in mathematical reasoning (Maloney, Risko, Ansari, & Fugelsang, 2010; Rubinsten & Tannock, 2010; Young, Wu, & Menon, 2012).

In the long term, low numeracy has been shown to result in reduced employment opportunities and high public costs underscoring the importance of understanding more about the development and the consequences of DD (Gross, 2009; Parsons & Bynner, 2005).

1.2.3 Etiology

To date, many factors are supposed to contribute to the aetiology of DD. Even if a multi-factorial model is supported from the current stage of research, little is known about the relationship and the interactions of the single factors. Genetic studies provide evidence for the heritability of DD, indicating that prevalence in affected families is almost tenfold higher than in the general population (Alarcon, DeFries, Light, & Pennington, 1997; Shalev et al., 2001). In several genetic syndromes arithmetical disability is reported as one of the core symptoms (e.g. fragile X syndrome). However, more recently published studies revealed that individual differences in number sense are mainly explained by non-shared environmental influences rather than by genetic factors (Kovas, Haworth, Petrill, & Plomin, 2007; Tosto et al., 2014), supporting the view that biological predisposition should not be regarded as deterministic.

1.2.4 Behavioural and neuronal deficits in DD

Accumulating knowledge has shown that children with DD display various deficits in numerical and arithmetical skills. Difficulties are already reported in basic numerical tasks such as writing and reading Arabic numerals (transcoding), magnitude processing and counting (Butterworth et al., 2011; Geary, Hamson, & Hoard, 2000; Ise & Schulte-Körne, 2013; Kucian & von Aster, 2014). Children with DD produce significantly more errors when processing numbers in the subiziting range (Landerl, 2013) indicating that they might count even small numerosities (Moeller, Neuburger, Kaufmann, Landerl, & Nuerk, 2009). Thus, difficulties in arithmetical knowledge are widely found in dyscalculic children. Most of the children encounter significant problems in learning and recalling arithmetical fact knowledge as well as understanding mathematical procedures (Geary, 2010; Geary, Hoard, Nugent, & Bailey, 2012). As a result, dyscalculic children often use immature strategies to solve arithmetical problems (e.g. finger counting).

Apart from the behavioural findings, evidence from neuroimaging studies reveals that DD may also have its origin in deficient neuronal mechanisms. Dysfunction in parietal regions, particularly in the intraparietal sulcus (IPS), is found in dyscalculic children during number and arithmetic processing (Ashkenazi, Rosenberg-Lee, Tenison, & Menon, 2012; Kucian et al., 2006; Kucian, Grond, et al., 2011; Mussolin, De Volder, et al., 2010; Price, Holloway, Räsänen, Vesterinen, & Ansari, 2007). This area is known to be the core region of number processing producing dyscalculic-similar behaviour when disrupted by transcranial magnetic stimulation (TMS) (Cappelletti, Barth, Fregni, Spelke, & Pascual-Leone, 2007; Cohen Kadosh et al., 2007). On the other hand, differences in regions of the frontal and occipital-temporal brain, attributed to general executive functions, working memory, and attention, are also found between typically and atypically developing children (Davis et al., 2009; Kaufmann et al., 2009, 2011; Kucian, Grond, et al., 2011; Rosenberg-Lee et al., 2014). In a meta-analysis, Kaufmann and co-authors (2011) conclude that children with DD increasingly rely on compensatory mechanisms, specifically, the recruitment of finger-based number representations. These results were confirmed when structural differences in grey and white matter were detected in individuals with DD. In particular, abnormal volumes and fibre connections have been found for parietal but also frontal, temporal and subcortical areas (Kucian et al., 2013; Rotzer et al., 2008; Rykhlevskaia, Uddin, Kondos, & Menon, 2009); for an overview see also Matejko and Ansari (2015).

Representation of quantity and numbers

The representation of quantity and numbers, which is a pivotal skill of numerical cognition, has been shown to be severely deficient in children with DD. Several studies report lower performance in the non-symbolic approximate number system (dot arrays) as well as in the exact symbolic system (Arabic numbers) (Desoete, Ceulemans, De Weerdt, & Pieters, 2012; Landerl, Fussenegger, Moll, & Willburger, 2009; Mussolin, Mejias, & Noël, 2010; Piazza et al., 2010). However, there have also been studies revealing that children with DD only seem to be impaired when comparing Arabic digits but not when comparing non-symbolic stimuli (Castro Cañizares, Reigosa Crespo, & González Alemañy, 2012; Defever, De Smedt, & Reynvoet, 2013; Rousselle & Noël, 2007). Rubinsten and Henik (2005) further conclude that Arabic numbers do not automatically activate representations of magnitude in dyscalculic subjects. This controversial discussion led to the formation of the hypothesis that children with DD may predominantly suffer from deficits in the approximate magnitude representation (Butterworth et al., 2011; Halberda, Mazzocco, & Feigenson, 2008a). Alternatively, it was hypothesised that the impairment lies in the failure to form an exact representation of numerical value by linking Arabic Symbols to numerical representations (Noel & Rousselle, 2011; Rubinsten & Henik, 2005).

A further aspect of the internal representation of numbers and quantity, regardless of being approximate or exact, is the spatial orientation and organisation in a mental number line (Berch et al., 1999; Dehaene, 2003). Dyscalculic children show a deficient and delayed spatial number representation on both the behavioural as well as the neuronal level (Geary, Hoard, Nugent, & Byrd-Craven, 2008; Kucian, Grond, et al., 2011; Landerl, 2013). In the study of Piazza and co-authors (2010) number acuity of 10-year-old dyscalculics was at a similar level as in 5-year younger non-dyscalculic controls. In addition, children with DD exhibited dysfunctional activation in the fronto-parietal network during a number order task (Kucian, Grond, et al., 2011). A number line training, conducted in the same study, led to improvements in the spatial representation of numbers and to a remediation of parietal brain activation, including the intraparietal sulcus (Kucian, Grond, et al., 2011).

Domain-general deficits in developmental dyscalculia

Domain-general abilities have been argued to contribute to the difficulties in DD. The rather heterogeneous clinical picture of DD and the high comorbidity rates corroborate the view for a multiple component explanation (see also Fias et al., 2013). A growing amount of evidence suggests that attention (Anobile, Stievano, & Burr, 2013; Askenazi & Henik, 2010), (visuo-spatial) working memory (Ashkenazi, Rosenberg-Lee, Metcalfe, Swigart, & Menon, 2013; Raghubar, Barnes, & Hecht, 2010; Rotzer et al., 2009), and motor skills (Pieters, Desoete, Roeyers, Vanderswalmen, & Van Waelvelde, 2012) are related to numerical and arithmetical achievement and shown to be dysfunctional in children with DD. Accordingly, it would be important to control well for those variables in studies and further to investigate the relation and interaction of those components in the development of numerical and arithmetical abilities.

1.3 Processing of numbers and space

The close relationship between numbers and space has often been discussed in numerical cognition, eventually leading to the theory that number, space, and time might be part of a generalised magnitude system (A Theory Of Magnitude, ATOM) (Bueti & Walsh, 2009; Walsh, 2003). Support for the ATOM-theory is found in an increasing number of studies in children and adults (Dormal, Andres, & Pesenti, 2012; Dormal, Dormal, Joassin, & Pesenti, 2012; Fias, Lammertyn, Reynvoet, Dupont, & Orban, 2003; Hurewitz, Gelman, & Schnitzer, 2006; Lourenco & Longo, 2010).

Spatial abilities have also been studied in children with DD. However, a closer look into current literature reveals that only a few studies investigated visuo-spatial abilities systematically and thoroughly. So far, results indicate a deficit in various visuo-spatial tasks such as in visuo-spatial perception, visuo-cognition, and visuo-construction (Landerl et al., 2009; Osmon, Smerz, Braun, & Plambeck, 2006; Pieters et al., 2012; Rourke & Finlayson, 1978). Skagerlund and Träff (2014) studied numerical, spatial and temporal processing providing evidence for deficits in all three measures. Significant group differences have also been reported for activation in the inferior parietal lobe in a spatial orientation task (Kaufmann et al., 2009). In line with these findings, Bachot et al. (2005) found abnormal number representation in children with visuo-spatial disabilities. However, some results are more contradictive; for instance, no differences in spatial abilities were reported in the work of Szucs et al. (2013). It is important to note that systematic studies are scarce and spatial abilities show a high diversity limiting the comparability of the studies. In summary, findings point to difficulties in visuo-spatial skills in children with mathematical disabilities.

1.4 Studying development

To date, most of the studies claiming to investigate development compare a group of adults to a group of children. Problematic with this approach is that results from this type of studies allow only to draw conclusions about neuronal commonalities or differences, but not about how development proceeds (Karmiloff-Smith, 2010). At first, activation of neuronal networks seems to be diffuse and more distributed. This subsequently develops into a more specialised and rather focussed pattern (Durston et al., 2006). Brain activation, therefore, differs between mature and developing brains which should be taken into account when studying neuronal development (Ansari, 2010; see also Emerson & Cantlon, 2014). Moreover, the lack of studies during puberty and adolescence has led to a gap in the knowledge over this crucial time in developmental.

Longitudinal studies are one possibility to answer questions about the gradual changes of brain functionality. They are, however, very time consuming and work-intensive. As a result, developmental questions are in many cases examined by more time-efficient methods.

1.5 Functional magnetic resonance imaging

1.5.1 The basis of the fMRI signal

After a long period of predominantly behavioural studies, functional magnetic resonance imaging (fMRI) is one of the remarkable tools to open the "black box" and study the relation between brain and behaviour. The discovery that oxygenated haemoglobin has diamagnetic, whilst deoxygenated haemoglobin has paramagnetic properties was the first step in direction of fMRI (Pauling & Coryell, 1936). When introduced in a magnetic field, deoxygenated haemoglobin affects magnetic susceptibility. This consequently causes rapid spin dephasing resulting in a shorter T2* signal in deoxygenated and a longer T2* signal in oxygenated haemoglobin (Ogawa, Lee, Nayak, & Glynn, 1990; Thulborn, Waterton, Matthews, & Radda, 1982). Ogawa and colleagues (1990) proposed that this blood-oxygenation-level depended (BOLD) contrast can further be used as indirect measure of changes in functional brain activity leading to the first fMRI studies in 1992 (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Kwong et al., 1992; Ogawa et al., 1992); see also the review by Raichle (2009).

1.5.2 Neurovascular coupling

The exact mechanisms of neurovascular coupling are not yet well understood. The BOLD signal bases on the assumption that an active brain area is supplied with more oxygenated blood, therefore leading to an increase in the MR signal (Logothetis, 2003; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). In addition to the ratio of the deoxygenated to oxygenated haemoglobin, this process further depends on the underlying mechanisms of the regional cerebral blood volume and flow (Fox & Raichle, 1986; Fox, Raichle, Mintun, & Dence, 1988). As a consequence, the BOLD signal is slightly delayed (3-8s) in relation to the onset of the neuronal response. This is characterised by an initial signal decrease (initial dip) due to the accumulated deoxygenated haemoglobin. The subsequent increase in oxygenated enriched blood flow and volume leads to the known fMRI BOLD signal (for more detailed information see also Huettel, Song, & McCarthy, 2004; Raichle, 2009).

1.5.3 Studying brain and behaviour

fMRI is a non-invasive technique and, therefore, allows to acquire images repetitively from the same subject. The obtained pictures are sufficient to perform statistical analysis on the data of one individual. Inter-subject averaging and further methodological progresses lead to the successful comparison between single subjects, building the basis of today's fMRI data processing (Fox, Mintun, Reiman, & Raichle, 1988; Fox, Perlmutter, & Raichle, 1985; Friston et al., 1989). The use of different experimental designs (e.g. block design, event-related designs) further enabled researchers to investigate more complex questions of cognition (Buckner et al., 1996, 1998; Friston, Frith, Liddle, & Frackowiak, 1991; Petersen, Fox, Posner, Mintun, & Raichle, 1988, 1989; Rosen, Buckner, & Dale, 1998).

Because of the good spatial resolution, the minimal risk, the absence of long-term effects, and the various possibilities to measure neuronal changes fMRI is a valuable tool to investigate children and development (Church, Petersen, & Schlaggar, 2010; Karmiloff-Smith, 2010). However, to the known disadvantages (e.g. low temporal resolution) researchers are additionally confronted with some challenges. Movement artefacts are problematic, particular in children, as they may lead to high exclusion rates and bias the group. Furthermore, developmental differences in vascular physiology are not well understood (Church et al., 2010; Karmiloff-Smith, 2010).

Nonetheless, fMRI is one of the most used neuroimaging techniques to examine and answer questions about the relation of brain and behaviour in development.

2 Longitudinal brain development of numerical skills in children with developmental dyscalculia

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Submitted to Brain, September 2014

2.1 Abstract

Developmental dyscalculia is a learning disability affecting the acquisition of numerical and arithmetical skills. In particular, children with developmental dyscalculia display early and persistent deficits in various number processing skills, known to be crucial for the development of subsequent arithmetic achievement. Even though there are several studies reporting aberrant functional activation of the fronto-parietal numerical network in dyscalculic children, little is known about the neuronal development of numerical abilities. In this study, we therefore investigated the neuronal development of children with and without developmental dyscalculia from a longitudinal point of view.

Seventeen children with developmental dyscalculia aged 8-11 years (14 girls) and 12 typically developing children aged 8-10 years (5 girls) were evaluated by means of neuropsychological tests and functional Magnetic Resonance Imaging over a 4-year period.

Over time, typically developing children improved in numerical abilities and showed a consistent and well developed fronto-parietal network. In contrast, children with developmental

dyscalculia revealed persistent deficits in number processing and arithmetical skills compared to their peers. Brain imaging results of the dyscalculic group showed an age-related activation increase in parietal regions (bilateral intraparietal sulcus), pointing to a delayed development of number processing areas. Secondly, an activation increase in frontal areas (insula, left inferior frontal gyrus) was observed over time, indicating a possible use of compensatory and emotional control mechanisms.

In conclusion, this study is the first to measure behavioural and neuronal trajectories of numerical abilities longitudinally in a group of typically developing and dyscalculic children. Results suggest a continuation in neuronal development of number representation in children with developmental dyscalculia, whereas the neuronal network for simple ordinal number estimation seems already established in typically achieving children at age 9.

2.2 Introduction

How does the "numerical brain" develop? Numbers are omnipresent in our lives and our innate ability to detect small numerosities enables us to develop complex mathematical skills at a young age (Izard et al., 2009; Starkey et al., 1990; Xu & Spelke, 2000). Not surprisingly, individuals with DD struggle in their everyday life. DD is a learning disability affecting the acquisition of numerical-arithmetical skills in children with normal intelligence and age-appropriate school education (WHO, 2010). Many studies have shown that children with DD display various deficits in number processing such as counting, magnitude processing, or spatial number representation (Landerl, 2013; Landerl, Bevan, & Butterworth, 2004; Mussolin, Mejias, et al., 2010; Rousselle & Noël, 2007). Those number processing skills are assumed to predict later arithmetical achievement (De Smedt, Verschaffel, & Ghesquière, 2009; Geary et al., 2012; Halberda, Mazzocco, & Feigenson, 2008b; Träff, 2013) and are therefore an essential step in the development of numeracy. Furthermore, DD has a relatively high prevalence of 3-7% (Gross-Tsur et al., 1996; Reigosa-Crespo et al., 2012; Wyschkon et al., 2009) and a persisting character (Shalev et al., 1998, 2005). The fact that difficulties in numeracy result in reduced employment opportunities and high public costs underscores the importance of understanding more about the development of the numerical brain (Gross, 2009; Parsons & Bynner, 2005).

One pivotal skill of number processing is the spatial representation of quantity and numbers, also known as the mental number line (Berch et al., 1999; Dehaene, 2003). The formation of such an internal representation is assumed to begin at early age and to be refined with entrance to school and acquisition of the symbolic number system (Ebersbach et al., 2008; Halberda & Feigenson, 2008; Siegler & Booth, 2004; von Aster & Shalev, 2007). Since linearity of the mental number line is correlated with arithmetical knowledge and predictive for learning unfamiliar arithmetic problems (Booth & Siegler, 2008), several studies reported that children with DD are less accurate in placing numbers on a number line (Geary et al., 2008; Landerl, 2013). Piazza and co-authors (2010) showed that number representation in children with DD is deficient and delayed, with 10-year-old dyscalculics performing at a similar level to 5-year-old typically developing (TD) children. These results are supported by neuroimaging findings demonstrating that children with DD show aberrant functional activation in number tasks compared to normally developing peers. Significant differences are mainly found in domain-specific regions of the parietal lobe, known to be important for magnitude processing and supposed to incorporate the mental number line (Ashkenazi et al., 2012; Kucian et al., 2006; Kucian, Grond, et al., 2011; Price et al., 2007). It has been widely reported that in children with DD, activation in parietal regions is reduced and lacks modulation with increasing task demands (Ashkenazi et al., 2012; Kucian et al., 2006; Kucian, Grond, et al., 2011; Mussolin, Mejias, et al., 2010; Price et al., 2007). However, a closer look into the literature reveals that findings are not consistent and some studies describe increased activation in DD compared to typically achieving children in these areas (Davis et al., 2009; Kaufmann et al., 2009, 2011). Additionally, activation differences are also found in domain-general regions mainly in the frontal brain, attributed to working memory, attention and planning (Davis et al., 2009; Kaufmann et al., 2009; Kucian et al., 2006; Kucian, Grond, et al., 2011; Price et al., 2007). To summarise, this aberrant brain activation pattern possibly reflects the typical deficiency in processing numerical magnitudes and the greater cognitive resources needed for solving the task.

From the developmental point of view, a number of cross-sectional studies have been conducted to investigate age dependent neuronal differences of numerical functions in typically achieving children. Findings in the literature suggest that children activate similar regions to adults in order to solve numerical tasks. However, children recruit parietal regions to a lesser extent, in particular the IPS, and show increased frontal activation compared to adults (Ansari & Dhital, 2006; Ansari et al., 2005; Cantlon, Brannon, Carter, & Pelphrey, 2006; Holloway & Ansari, 2010; Kucian et al., 2008). In addition to the specialisation for the abstract representation of numerical magnitude, the IPS was found to become increasingly sensitive to the semantics of numerical symbols over time (Holloway & Ansari, 2010). According to these findings, researchers hypothesised that there is a shift from an initially controlled and effortful (frontal activation) to a subsequently more automatic processing of numerical magnitude (parietal activation) (Ansari et al., 2005; Holloway

& Ansari, 2010; Kucian et al., 2008; Rivera et al., 2005). Conversely, Rosenberg-Lee et al. (2011) reported an increase in parietal, but also prefrontal and visuo-temporal regions over a 1-year period in children solving arithmetic problems, suggesting a nonlinear trajectory of developmental changes.

Secondly, several behavioural long-term studies investigated the development of typical and atypical number processing, showing that its efficiency is a good predictor for later arithmetical achievement (Desoete et al., 2012; Geary et al., 2012; Halberda et al., 2008b; Landerl, 2013; Passolunghi & Lanfranchi, 2012; Reigosa-Crespo et al., 2013; Träff, 2013). Landerl et al. (2013) followed children's numerical abilities over a 2-year period and found that even if dyscalculic children showed improvements during elementary school years, numerical processing remains persistently deficient. Anomalies were found in the subitizing range of dot enumeration, placing numbers on a number line task and processing two-digit numbers. Further studies revealed that those deficits are already detectable in kindergarten and persist into adolescence, with most of the children showing stable performance and scoring in the lowest quartile of their grade over time (Geary et al., 2013; Mazzocco et al., 2013; Shalev et al., 1998, 2005; Stock, Desoete, & Roeyers, 2009). In addition, low achievement in math has been linked to math anxiety, suggesting that children with DD have increased math anxiety scores compared to TD peers (Ma, 1999; Rubinsten & Tannock, 2010).

To date, the current body of research has identified a substantial deficit in numerical processing in children with DD, indicating that there is a functional specialisation in the areas thought to support numerical magnitude processing. Nevertheless, little is known about the neuronal development of numerical abilities. As Ansari (2010) stresses in his review, only children within a certain age range have been tested, and comparisons between TD and dyscalculic children at different time points or longitudinal studies are lacking. Furthermore, a considerable number of findings are based on studies with adults and should be interpreted carefully with respect to children and development. It is important to take into account that activated networks differ between mature and developing brains and deficiencies might vary over time and with development. Most of the studies in the last decade either investigated the development of typical and atypical number skills solely from a behavioural point of view or neglected to look at children with DD when investigating neuronal development.

2.3 Aim and hypotheses

Hence, the goal of the present study was to investigate the typical and atypical neuronal development of numerical abilities by means of longitudinal fMRI and behavioural data. By measuring the same subjects twice it is possible to take into account the heterogeneity of DD and assess “purer” developmental effects, relative to those inferred from cross-sectional designs.

Based on the previous literature, we hypothesise deviant activation of the fronto-parietal network and lower behavioural performance in children with DD (Kucian et al., 2006; Kucian, Grond, et al., 2011; Price et al., 2007). In typically achieving children, developmental effects are expected to be found in an increase in activation in the number-specific parietal regions and a decrease of activation in the domain-general regions reflecting the growing proficiency in number processing (Ansari & Dhital, 2006; Cantlon et al., 2006; Holloway & Ansari, 2010). To our knowledge there are no studies about the neuro-functional development of children with DD. Consequently, predictions about the results of the atypical development are speculative. However, according to the behavioural deficits and the differences in the neuronal correlates of number processing, we expect a delayed developmental pattern in dyscalculic children. In particular, we anticipate a persistent deficiency in numerical processing along with constant lower parietal activity compared to children without DD. Furthermore, higher frontal activation over time is predicted in DD children, as requirements of cognitive resources may change in consequence of a developmental delay.

2.4 Methods

2.4.1 Study design and participants

In this longitudinal study, a group of children with DD and a group of TD children were evaluated by neuropsychological tests and fMRI (baseline). After 4.2 (SD = 0.46) years, children returned for a second neuropsychological and fMRI assessment (follow-up).

In total 35 children between 8 and 11 years were recruited into this study, of which 25 took part in a previous study (Kucian, Grond, et al., 2011). Inclusion criteria for all children were an IQ > 85 and no diagnosis of a neurologic or psychiatric disorder. Additionally, DD children had to perform in the lowest 10 percent of a standardised numerical test battery at the entry of the study. In contrast, TD children had an age-appropriate mathematical performance at baseline and follow-up assessment. Accordingly, six DD children and one TD child were excluded. The behavioural data analyses are therefore based on 17 DD and 11 TD children. Groups did not differ in terms of age, gender and handedness (Table 2.1). Informed consent was obtained from participants when 16 years of age or older and all parents. The study was approved by the local ethics committee based on guidelines from the World Medical Association's Declaration of Helsinki (WMA, 2002). For the fMRI analysis, four data sets at baseline and eight at follow-up were excluded because of task performance <50%, scanner problems or poor image quality due to artefacts from braces. Hence, subsequent statistical group comparisons are based on 14 baseline and 13 follow-up fMRI data sets for DD and 11 baseline and 8 follow-up data sets for TD children.

2.4.2 Behavioural testing

All children completed neuropsychological testing. Most of the tests were performed at both time points. However, some tests had to be replaced because norm data were not available in the target age groups (see Table 2.1).

Table 2.1 Demographic characteristics and neuropsychological test scores.

Measure	**Dyscalculic children**		**Typically developing children**		**Test-statistics**	**p-value**
	M	**SD**	**M**	**SD**		
Baseline assessment						
Age	9.6	0.8	9.1	0.9	1.506[a]	0.144
Gender m/f	3/14		6/5		4.169[b]	0.095
Handedness l/a/r	2/5/10		1/3/7		0.081[b]	0.999
Numerical abilities						
ZAREKI-R	12.5	16.3	77.0	19.1	-8.940[a]	<0.001
WISC-III Arithmetic	91.9	8.7	107.3	13.5	-3.337[a]	0.004
Domain general cognitive abilities (WISC-III)						
Similarities	104.4	8.6	114.5	8.8	-3.011[a]	0.006
Block Design	93.2	12.9	115.5	9.3	-4.935[a]	<0.001
Picture Arrangement	103.1	14.1	105.0	12.8	-0.351[a]	0.728
Vocabulary	100.9	8.3	114.1	8.3	-4.099[a]	<0.001
Estimated general IQ	100.4	6.4	112.3	6.9	-4.649[a]	<0.001
Memory (BTT)						
Visuo-spatial memory span	4.4	0.6	4.6	0.9	0.464[c]	0.595
Visuo-spatial working memory	2.9	1.8	3.7	1.0	0.532[c]	0.425
Follow-up assessment						
Age	13.8	1.0	13.5	0.9	0.803[a]	0.429
Numerical abilities						
BASIS-MATH 4-8	52.2	9.4	76.0	4.6	-7.799[a]	<0.001
KFT 4-8+R Quantity Comparison	41.3	3.4	54.6	5.9	-6.899[a]	<0.001
Domain general cognitive abilities (WISC-IV)						
Similarities	103.8	8.6	113.2	5.6	-3.195[a]	0.004
Block Design	96.8	15.2	109.6	7.9	-2.913[a]	0.007
Matrix Reasoning	105.0	8.5	116.8	9.8	-3.387[a]	0.002
Estimated general IQ	101.9	7.3	113.2	5.4	-4.405[a]	<0.001
Memory (BTT, WISC-IV)						
Visuo-spatial working memory	5.6	1.7	7.0	2.0	1.161[c]	0.039
Verbal memory span	5.6	1.1	6.0	0.9	0.594[c]	0.384
Verbal working memory	4.4	1.0	5.0	1.0	0.608[c]	0.399
Attention (TAP)						
Alertness	46.4	10.5	46.7	9.9	-0.069[a]	0.946
Go-nogo	63.0	31.2	66.2	24.5	0.479[c]	0.913
Go-nogo error rate	16.6	20.5	19.0	16.8	0.740[c]	0.412
Reading (SLRT-II)						
Words					12.283[b]	0.765
Pseudowords					11.540[b]	0.619

ZAREKI-R = Neuropsychological Test Battery for Number Processing and Calculation in Children [PR], WISC = Wechsler Intelligence Scale for Children [IQ-Score], BTT = Block-Tapping-Test, BASIS-MATH 4-8 = Basic Diagnostic in Mathematics Education for Grades 4-8, KFT 4-8+R = Cognitive Abilities Test [T-score], TAP = Testbattery for Attentional Performance [PR], SLRT-II = Salzburg Reading and Orthography Test

[a] t-Test, [b] Fisher's Exact Test, [c] Kolmogorov-Smirnov-Z Test

Arithmetical achievement

At baseline, numerical abilities were assessed using the revised version of the Neuropsychological Test Battery for Number Processing and Calculation in Children (ZAREKI-R) (von Aster, Weinhold Zulauf, & Horn, 2006). This test battery consists of 11 subtests and tends to differentiate in the lower range of numerical abilities. Therefore, this test was used to identify children with DD, which is the case when scoring 1.5 SD below average.

At the follow-up assessment the test for Basic Diagnosis in Mathematics Education for Grades 4-8 (BASIS-MATH 4-8) (Moser Opitz et al., 2010) was used. The test battery is composed of three difficulty levels measuring several arithmetical abilities. Criteria for DD were met if the performance was under a threshold value of 67 points (out of a total of 83 points).

Additionally, the subtests Arithmetic of the Wechsler Intelligence Scale for Children (WISC-III) (Tewes, Rossmann, & Schallberger, 1999) and Quantity Comparison of the Cognitive Abilities Test (KFT 4-8+R) (Heller & Perleth, 2000) were used at the baseline and follow-up assessment respectively to be able to compare children's mathematical performance at the peer level.

The spatial representation of numbers was measured by means of a paper-and-pencil number line task. Children had to estimate the position of 20 Arabic digits on a left to right oriented number line with the labelled end points 0 and 100. Each number had to be marked on consecutive number lines to avoid the possibility of comparisons between items.

Finally, children solved 40 simple addition and subtraction problems. The items ranging from 1 to 100 were balanced for frequency of digits and bridging decades.

At the follow-up assessment a computerised and age-adapted version of the test was used. In the number line task the position of the number was indicated by mouse-click and/or arrow keys. Arithmetic problems were solved by typing the solution using the keyboard. To prevent ceiling effects, the number line task and the arithmetic problems were expanded to numbers up to 1000.

Intelligence quotient and comorbid disorders

Handedness was determined by the Edinburgh Handedness Inventory (Oldfield, 1971).

Intelligence was measured with the third, respectively fourth edition of the WISC (Petermann & Petermann, 2007; Tewes et al., 1999). Table 2.1 shows the estimated general IQ and the results of the subtests (WISC-III: Similarities, Block Design, Vocabulary, Picture Arrangement; WISC-IV: Similarities, Block Design, Matrix Reasoning).

Verbal and visuo-spatial memory span as well as working memory was assessed in order to control for memory effects. At baseline memory span and working memory were measured with the Block-Tapping-Test (Schellig, 1997) and the Block-Suppression-Test (Beblo, Macek, Brinkers, Hartje, & Klaver, 2004). At the follow-up assessment the subtest Digit Span of the WISC-IV (Petermann & Petermann, 2007) was additionally performed.

Levels of attention and inhibition were measured at the follow-up by means of the subtests Alertness and Go-nogo of the Testbattery for Attentional Performance (TAP) (Zimmermann & Fimm, 1993).

The 1-Minute-Reading-Task from the Salzburg Reading and Orthography Test (Moll & Landerl, 2010) was used to estimate the reading performance and control for dyslexia. Because of lacking test norms in grades 7 and 8, values were obtained by interpolating the norms from the test manual (grade 6) and from Kronschnabel et al., (2013) (grade 9).

2.4.3 fMRI task

The paradigm is adopted from Kucian et al. (2011) and intends to measure spatial number representation. The entire paradigm lasted 10.5 minutes and consisted of four blocks of a numerical order task (experimental condition) alternating with four blocks of a number identification task (control condition). Blocks were counter-balanced between subjects. At the beginning of each block an instruction was shown for 2s, followed by 10 trials of one of the two conditions and a rest period with a fixation cross for 20s, resulting in a total block length of 59.5s. Every stimulus was presented for 2s, followed by a blank screen with an inter-stimulus-interval jittered between 3 and 5s.

A stimulus consisted of three Arabic digits between “1” and “9” (horizontally aligned) shown simultaneously via a video goggles system (VisuaStimDigital, Resonance Technology Inc., USA). In the experimental condition children had to decide if the numbers were in ascending/ descending order or not in order respectively. The same stimuli were presented in a randomised order in the control condition, in which children had to indicate if the number “2” was present or not. The children answered by a button press of the dominant hand (index finger for “yes”, middle finger for “no”), which was recorded using an MRI compatible response box (Lumina Respond Pad, Cedrus Corporation, USA). The paradigm was programmed on E-Prime (Version 2, Psychology Software Tolls Inc., USA).

2.4.4 Image acquisition

MRI data were acquired on a 3T General Electric Signa Scanner (GE Medical Systems, USA) using an 8-channel head coil. Whole brain functional images were acquired interleaved with a gradient echo EPI sequence (36 slices, 3.4mm slice thickness (ST), no interslice skip, 64x64 matrix size (MS), field of view (FOV) = 220mm, flip angle (FA) = 45°, echo time (TE) = 31ms, repetition time (TR) = 2100ms). Additionally, a T1-weighted structural image was obtained with a fast spoiled gradient echo sequence (3D FSPGR, ST = 1mm, no interslice skip, MS = 256x192, FOV = 240mm, FA = 20°, TE = 2.912ms, TR = 9.972ms).

Participants were carefully instructed and supplied with hearing protection before entering the scanner. To minimise head motion, the head was stabilised with padding.

2.4.5 Data analysis

Behavioural data

Behavioural data was statistically analysed with SPSS (Version 20). To assess group differences parametric t-tests for independent samples or non-parametric Kolmogorov-Smirnov-Z-test were performed. A mixed-model ANOVA (analysis of variance) with time (baseline/follow-up) as within-subject factor and group (DD/TD) as between-subject factor was conducted to examine developmental effects.

fMRI preprocessing

The data were analysed by means of Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for NeuroImaging, UK) running under Matlab (Release 2012b, The MathWorks Inc., USA).

Three dummy scans, acquired to stabilise magnetisation at the beginning of the scan, were excluded from the analysis. Afterwards, the subjects' functional scans were realigned with rigid body transformations using the mean image as a reference scan. Six motion parameters were stored and included later in the analysis to control for motion. The mean functional image was then coregistered to the subjects' T1-weighted anatomical scan. In a next step, the individual anatomical scan was segmented into grey (GM) and white matter (WM) according to tissue probability maps of a paediatric atlas (NIH Paediatric Database) (Fonov et al., 2011; Fonov, Evans, McKinstry, Almli, & Collins, 2009). Parameters from the coregistration and segmentation were applied to the functional scans to normalise images into MNI (Montreal Neurological Institute) space. Finally, the functional images were smoothed with a Gaussian kernel of 6mm FWHM (full width half maximum).

fMRI statistics

The first level analysis was performed using a mass-univariate approach based on the GLM (General Linear Model). The time series from each subject were modelled with an event related design for the experimental and control condition using a canonical HRF (hemodynamic response function). The six subjects' motion parameters were entered as additional regressors. Slow signal drifts and serial correlations were accounted for by using a high-pass filter of 180s and a first level autoregressive model during maximum-likelihood estimation of the GLM parameters.

At the group level, a full factorial analysis with the factors group and time as well as IQ as a covariate was conducted for the contrast experimental-control condition. For the factor time (repeated measurement), within subjects correlations were accounted for by estimating the covariance and accordingly adjust the statistics and degrees of freedom during inference.

Statistical results are shown at a significance level of $p < .001$, corrected for multiple comparisons using a cluster-extent threshold of $k \geq 19$ voxels ($513mm^3$). Alternatively, results are presented with a less strict significance level of $p < .005$ and a cluster-extent threshold of $k \geq 22$ ($594mm^3$). According to Slotnick (2008), the spatial autocorrelation of the data was estimated. Then a Monte Carlo simulation was run with 10’000 iterations, using a type I error voxel activation probability of .001, and an estimated FWHM as a Gaussian smoothing kernel in order to derive the cluster extent threshold yielding the desired correction for multiple comparisons at a $p < .05$ level (Slotnick, 2004).

Anatomical localisation of the fMRI results was attained through the SPM Anatomy Toolbox (Eickhoff et al., 2005, 2007) and is reported in the MNI coordinate space.

2.5 Results

2.5.1 Behavioural data

Arithmetical achievement

Numerical abilities, assessed by ZAREKI-R and Basis-Math, differed significantly between DD and TD children at baseline and follow-up (Zareki-R: $p < .001$, effect size $r = .89$; Basis-Math: $p < .001$, $r = .84$) (Table 2.1). All children in the dyscalculic group still fulfilled the diagnostic criteria for dyscalculia at the follow-up. Moreover, a closer look at the Basis-Math data revealed that the DD group differed significantly in all three difficulty levels of the test (all $p < .001$), still showing a substantial deficit in the very basic arithmetical skills at a mean age of 13.8 years. Not surprisingly, DD children also performed significantly worse than the TD group in the tests measuring arithmetical skills at a peer level (Arithmetic of the WISC-III: $p = .004$, $r = .64$; Quantity Comparison of the KFT 4-8+R: $p < .001$, $r = .83$).

In the number line task, accuracy was measured by calculating the percentage distance from the marked to the correct position of the given number. A mixed-design ANOVA with time as within-subject factor and group as between-subject factor showed a significant effect of group ($p = .002$, $r = .43$) for the number line test 0 to 100 (Table 2.2)[1]. Children with dyscalculia placed the numbers further away from the correct position compared to the TD group. There was also a significant main effect of time ($p < .001$, $r = .61$), showing that accuracy increased with development. Finally, the significant interaction time by group indicated that DD children improved more over time than TD children ($p = .032$, $r = .24$). The additional number line test from 0 to 1000

[1] Data analysis based on 9 DD and 10 TD children.

Table 2.2 Behavioural results for the spatial representation of numbers (number line task), arithmetic (addition and subtraction) and the fMRI task.

Measure		**Dyscalculic children**		**Typically developing children**		**Effects of group**	**p-value**	**Effects of time**	**p-value**	**Interaction group x time**	**p-value**
		M	**SD**	**M**	**SD**						
Number Line Task (% distance)											
1-100[1]	T1	10.6	4.3	5.6	1.2	13.024[a]	0.002	26.424[a]	<0.001	5.444[a]	0.032
	T2	5.1	1.2	3.5	2.2						
1-1000	T2	9.4	5.8	4.1	2.3	1.506[b]	0.011				
Arithmetic											
Addition Accuracy[1]	T1	14.2	4.3	19.2	0.9	17.917[a]	0.001	0.018[a]	0.896	0.373[a]	0.549
	T2	15.0	4.7	18.7	1.4						
Subtraction Accuracy[1]	T1	13.3	2.5	17.4	1.8	24.066[a]	<0.001	0.066[a]	0.801	0.502[a]	0.489
	T2	12.9	4.4	18.2	1.5						
Addition RT (s)	T2	19.4	11.1	13.2	2.9	2.193[c]	0.041				
Subtraction RT (s)	T2	18.2	4.9	14.4	3.2	2.421[c]	0.023				
fMRI Paradigm											
fMRI Paradigm											
Accuracy (%)	T1	74.9	12.8	84.5	11.2	4.296[a]	0.049	40.847[a]	<0.001	1.949[a]	0.176
	T2	91.9	6.2	95.4	4.2						
RT (ms)	T1	1718	372	1615	280	1.910[a]	0.180	50.453[a]	<0.001	0.433[a]	0.517
	T2	1331	278	1261	255						

[a] Mixed-design ANOVA, [b] Kolmogorov-Smirnov-Z Test, [c] t-Test

[1] Data analysis based on 9 developmental dyscalculia and 10 typically developing children

performed at the follow-up assessment also revealed lower performance for the DD than the TD group ($p = .011$, $r = .56$).

For the simple addition and subtraction problems, the number of correctly solved items was quantified. ANOVAs revealed significant main effects of group with TD children solving more arithmetic problems correctly (addition: $p = .001$, $r = .51$; subtraction: $p < .001$, $r = .60$) (Table 2.**2**)[2]. No main effect of time or interaction could be found, due to adapting the difficulty of the task between the baseline and follow-up assessment.

Regarding the measured reaction times (RT) at the follow-up assessment, no significant differences could be found in the number line tasks between groups (all $p > .05$). However, children with DD took longer to solve the addition ($p = .041$, $r = .45$) as well as the subtraction problems ($p = .023$, $r = .44$) compared to their peers.

Intelligence quotient and comorbid disorders

All participants reached normal range of intelligence during both assessments (baseline: IQ = 93-125 follow-up: IQ = 92-122). However, groups differed significantly in the estimated general IQ and the single subtests except for Picture Arrangement (Table 2.1). Differences in IQ scores between a group of children with learning disabilities and a control group are often reported in the literature (Geary et al., 2000; Willcutt et al., 2013). Furthermore in the validation study of the WISC-IV handbook children with learning disabilities score significantly lower in several subtests compared to a control group (Petermann & Petermann, 2007). One reason for this is that IQ-tests are not independent from numerical skills. The IQ was not entered as a covariate in the subsequent behavioural analysis, since IQ is not independent from the effects of interest (Dennis et al., 2009; Field, 2009; Miller & Chapman, 2001).

[2] Data analysis based on 9 DD and 10 TD children.

In terms of controlling for comorbid ADD/ADHD and dyslexia, groups did not differ significantly in any measurement of attention or reading performance (Table 2.1). Regarding memory span and working memory, subjects showed at baseline and follow-up comparable results in the verbal as well as visuo-spatial memory component. The only significant difference was found in visuo-spatial working memory at the follow-up assessment due to lower performance of children with DD compared to TD ($p < .05$).

Behavioural results from fMRI task

RT smaller than 300 ms and misses were not included in the analyses of the paradigm. For the accuracy, the ANOVA revealed a significant effect of time ($p < .001$, $r = .63$), showing that children were better able to solve the task with increasing age (Table 2.2). Furthermore, the DD group performed significantly worse than the TD group ($p = .049$, $r = .15$). This significant difference arises mostly from their lower performance in the number order task ($p = .044$), as performance in the control task was comparable between groups ($p = .209$). The group by time interaction was not significant ($p = .176$, $r = .08$).

For the RT no effects of group or interaction between group and time was evident, all $p \geq .18$. However, children solved the task faster at the second assessment point ($p < .001$, $r = .68$).

2.5.2 fMRI group differences

At the baseline assessment, TD children showed typical fronto-parietal activation of the number processing network for the simple main effect (experimental minus control condition). On the other hand, children with DD showed discernibly lower activation in this known network (Figure 2.1, Table 2.3).

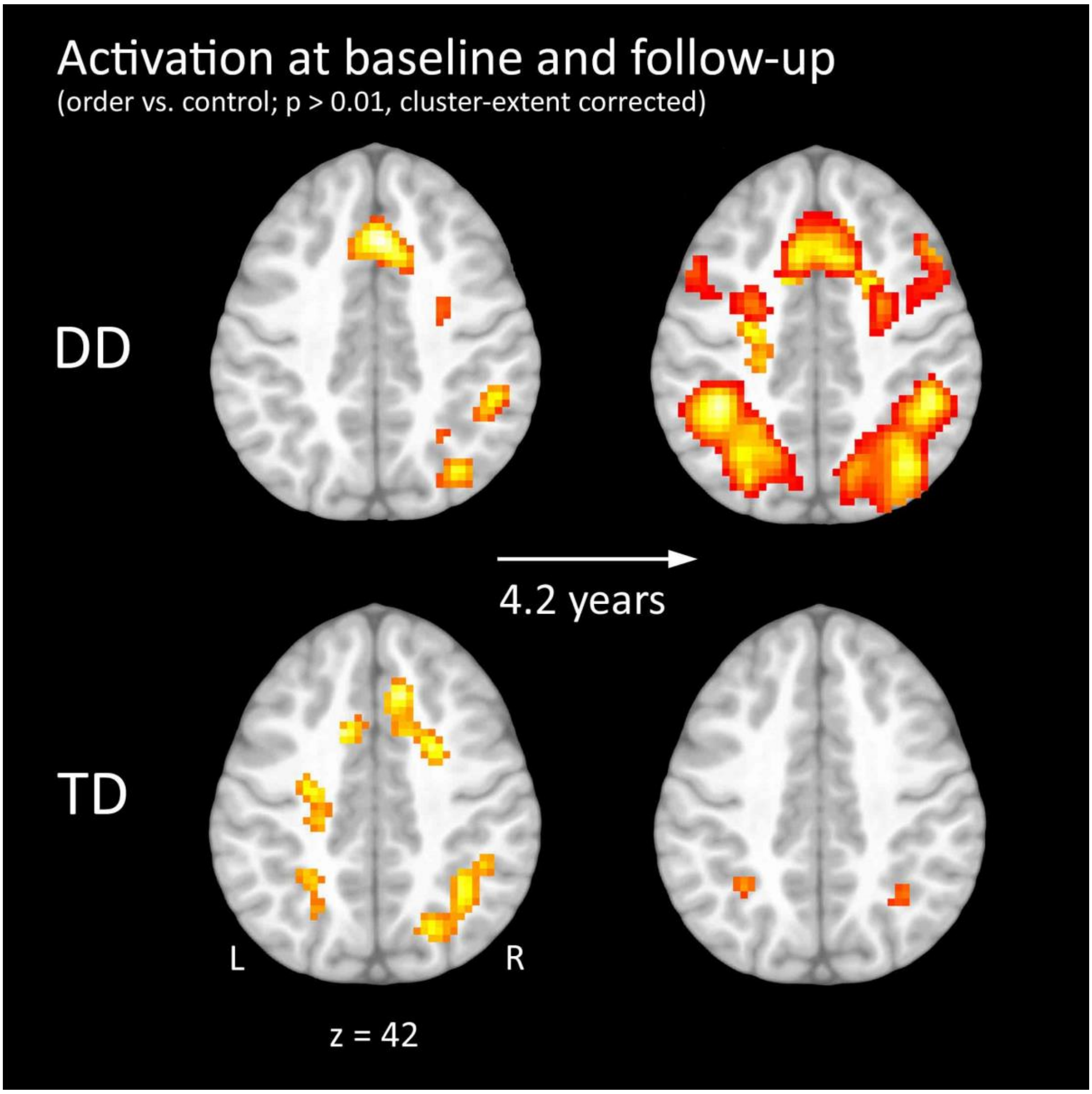

Figure 2.1 Task related brain activation shown on a paediatric template (Fonov et al., 2011, 2009) for the contrast order vs. control task at the baseline (left) and follow-up (right) measurement for children with developmental dyscalculia (upper row) and typically developing children (lower row).

Table 2.3 Brain areas that showed significant activation for the order vs. control task from dyscalculic and typically developing children for the baseline and follow-up assessment ($p < .01$, $k \geq 24$, cluster-extend corrected).

Region	Cluster size	Peak t-value	Peak MNI coordinates x	y	z
Baseline assessment					
Dyscalculic children					
L superior medial gyrus	203	5.21	1	22	42
Cerebellar vermis	143	4.65	1	-56	-36
L cerebellum	131	4.56	-32	-59	-36
R middle occipital gyrus	87	4.42	31	-71	39
R cerebellum	178	4.27	34	-56	-42
R intraparietal sulcus	173	4.12	43	-41	36
R precentral gyrus	43	3.64	49	1	24
R middle frontal gyrus	153	3.63	31	-2	54
Cerebellar vermis	34	3.48	4	-47	-15
R insula	35	3.33	31	19	6
R calcarine gyrus	71	3.26	31	-62	6
Typically developing children					
L precentral gyrus	175	4.46	-29	-14	48
L middle occipital gyrus, intraparietal gyrus	182	4.21	-26	-71	24
R superior occipital gyrus, intraparietal gyrus	276	4.20	22	-74	36
Middle cingulate cortex, SMA	630	4.17	-14	10	39
L insula	55	3.88	-35	13	6
R inferior frontal gyrus	25	3.64	52	7	18
L calcarine gyrus	83	3.55	-17	-80	9
Thalamus	27	3.04	-2	-20	6
Follow-up assessment					
Dyscalculic children					
L cerebellum	7531	6.98	-32	-62	-36
L inferior parietal lobe		5.44	-41	-44	45
R middle occipital gyrus, supramarginal gyrus	1190	6.20	34	-68	39
R inferior temporal gyrus	61	3.95	58	-44	-15
R calcarine gyrus	199	3.91	31	-77	3
L inferior frontal gyrus	35	3.44	-47	40	-6
Typically developing children					
L caudate nucleus	179	5.31	-17	-14	27
L hippocampus	155	4.83	-29	-65	0
L cerebellum, cerebellar vermis	252	4.59	1	-41	-42
L thalamus	103	4.22	1	-20	6
N/A	52	4.12	1	7	18
L cerebellum	63	3.95	-26	-65	-33
R hippocampus	40	3.88	25	-38	15
R caudate nucleus	75	3.70	10	-14	21
L intraparietal sulcus	25	3.20	-32	-53	42
R intraparietal sulcus	25	2.98	34	-59	45

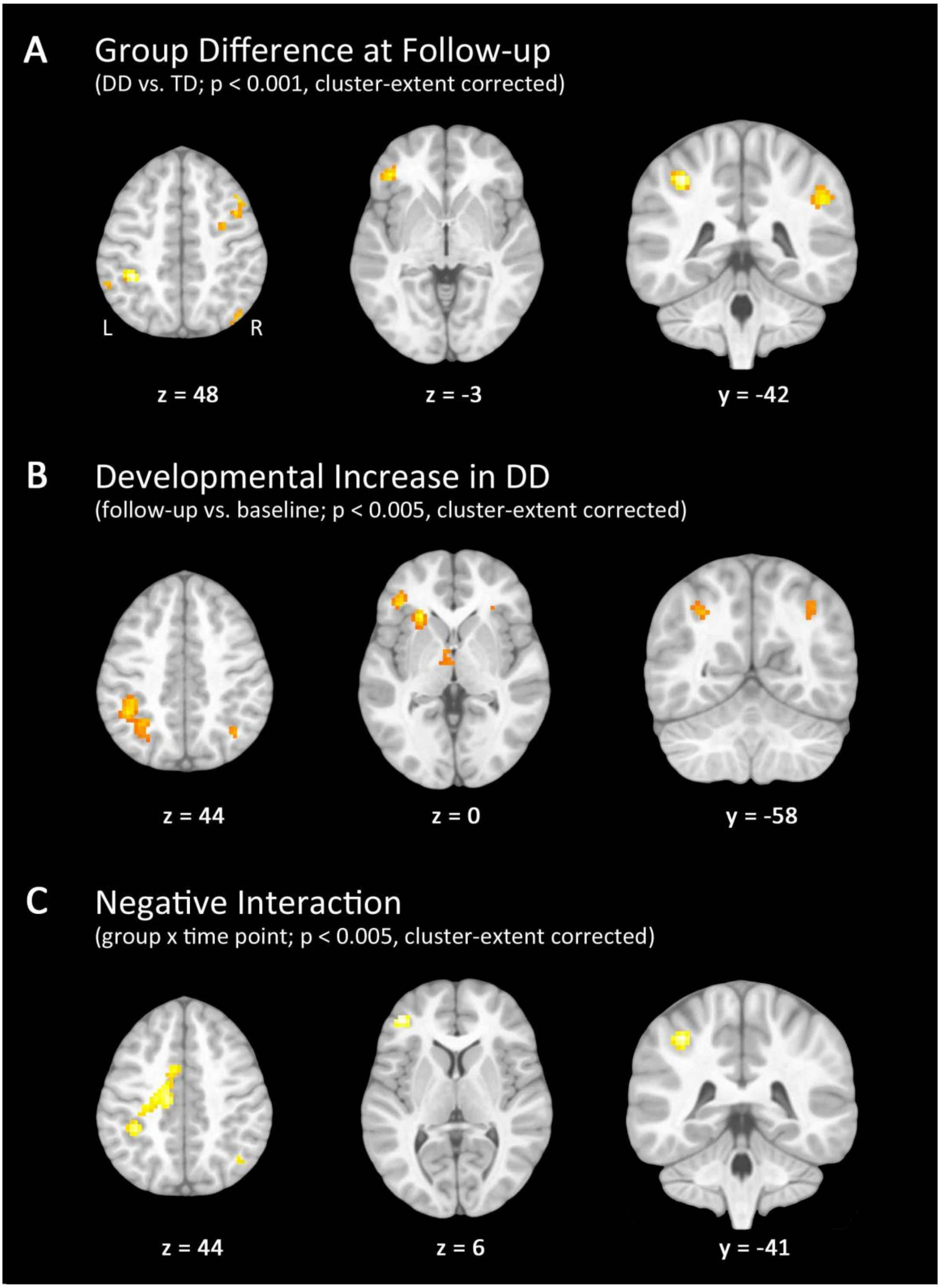

Figure 2.2

(A) Group differences: Increased activation in the dyscalculic compared to the typically developing group at the follow-up assessment (post-hoc t-test for the contrast DD vs. TD, p<.001, k≥ 19). (B) Developmental effects: Increase in brain activation in the dyscalculic group over developmental time (post-hoc t-test for the contrast follow-up vs. baseline, p<.005, k≥ 22). (C) Negative interaction: Activation increase over time was more pronounced in children with dyscalculia compared to typically developing children (group by time interaction, p<.005, k≥ 22).

Table 2.4 Brain areas that showed significant activation for the contrast dyscalculic vs. typically developing children at the follow-up assessment (p < .001, k ≥ 19, cluster-extend corrected).

Region	**Cluster size**	**Peak t-value**	**Peak MNI coordinates**		
			x	**y**	**z**
Group differences at the follow-up assessment					
L intraparietal sulcus	37	5.56	-38	-41	48
R middle frontal gyrus, precentral gyrus	65	4.39	43	19	45
L middle frontal gyrus	36	4.38	-29	4	63
R angular gyrus	55	4.33	40	-71	42
L inferior frontal gyrus	49	4.15	-44	37	-3
R supramarginal gyrus	45	4.14	49	-44	33
L angular gyrus, supramarginal gyrus	49	3.82	-53	-53	42
L angular gyrus	21	3.40	-38	-68	42

Table 2.5 Brain areas that showed significant developmental changes in children with developmental dyscalculia and the negative interaction group by time (p < .005, k ≥ 22, cluster-extend corrected).

Region	**Cluster size**	**Peak t-value**	**Peak MNI coordinates**		
			x	**y**	**z**
Developmental increase in DD					
Mamillary bodies, fornix	137	4.96	-2	-11	-18
L insula	78	4.35	-29	25	-6
L intraparietal sulcus	176	3.81	-23	-50	33
R putamen, insula	61	3.75	28	7	-12
L parahippocampal gyrus	34	3.62	-26	-14	-27
L inferior frontal gyrus	39	3.59	-41	34	-3
L thalamus	32	3.31	1	-17	6
R intraparietal sulcus	23	3.17	37	-62	45
Negative interaction group x time point					
L inferior frontal gyrus	60	3.99	-41	43	6
L inferior parietal sulcus	58	3.96	-38	-41	48
L middle cingulum	134	3.90	-38	-29	33
L hippocampus	24	3.68	-29	-14	-30
R middle occipital gyrus, angular gyrus	22	3.16	34	-62	36

At the follow-up assessment, two-sample t-tests revealed significant differences between children with DD and controls (Figure 2.2 A, Table 2.4). Children with DD showed increased activation in frontal areas including bilateral middle frontal gyri (MFG) and the left inferior frontal gyrus (IFG). In the parietal lobe, children with DD demonstrated more activation in the bilateral angular gyri (AG), extending into the supramarginal gyri (SMG) and the left IPS. No other difference between groups was found at the same statistical threshold.

2.5.3 fMRI developmental effects

Regarding development across both groups, an increase of brain activation in the right hippocampus was evident (main effect of time). Interestingly, no decrease in activation was found between baseline and follow-up assessment. Post-hoc t-tests revealed that developmental changes took place in the DD group, showing increased activation in the mamillary bodies and the left insula at $p < .001$. After lowering the threshold to $p < .005$, additional activation increases in the bilateral IPS, right insula, left IFG, left parahippocampal gyrus (PHG) and left thalamus were observed (Figure 2.2 B, Table 2.5).

The negative interaction time by group indicated that the activation increase over time was more pronounced in children with DD than in TD children. The left IFG was the only region showing interaction effects at the higher cluster-extent threshold ($p < .001$). Lowering the threshold ($p < .005$) revealed activation in similar regions to the t-test in DD during development, namely in the left middle cingulum extending into somatosensory area, left IPS, left hippocampus, and right AG (Figure 2.2 C, Table 2.5).

A regression analysis across both groups provided further support for our results, indicating that children who solved fewer arithmetic problems correctly at baseline showed more activation increase over time (see supplementary material in Appendix A).

2.6 Discussion

In the present study, we utilised a longitudinal design to investigate the neuro-functional development of children with and without DD by means of neuropsychological tests and functional MRI. In line with previous studies, we found that children with DD improved over time, but nonetheless showed persistent deficits in number processing and arithmetical skills when compared to their peers. In TD children, brain imaging results point to a consistent and well developed fronto-parietal network. In contrast, dyscalculic children show an increase in frontal and parietal brain activation over time possibly reflecting maturation processes but also a more effortful and inefficient use of the numerical network.

2.6.1 Deficient numerical processing and disrupted neuronal networks

As hypothesised, we found considerable deficits in number processing and arithmetic abilities in children with DD compared to a peer group. The more pronounced inaccuracy in a number line task is typically found in dyscalculics and is consistent with a large body of research findings (Geary et al., 2012, 2008; Landerl, 2013; Piazza et al., 2010). In addition, the accuracy in a number line task is thought to reflect a better magnitude representation (Ebersbach et al., 2008; Siegler & Booth, 2004). Therefore, our data point to a deficient magnitude representation in 9-year old and 14-year old dyscalculic children in the number range between 0-100. Consistent with the study from Piazza et al. (2010), the children with DD performed at the same level as the control group 4-years younger. Given that numerical magnitude representation further influences arithmetical learning, it is in good agreement with earlier studies (Booth & Siegler, 2008) that our DD group also showed poor performance in simple addition and subtraction problems.

Regarding brain activation, differences were only evident at the follow-up assessment. Children with dyscalculia showed increased activation in the entire numerical network compared to their peers. At this juncture, research findings are not consistent, showing reduced activation in parietal key regions for numeracy (Kucian, Grond, et al., 2011; Mussolin, De Volder, et al., 2010;

Price et al., 2007), but also reporting increased activation in parietal regions (Kaufmann et al., 2009; Kucian, Loenneker, Martin, & von Aster, 2011). Moreover, studies are mostly based on investigation of children within an age range of 7 to 12 years. Therefore they are only partially comparable to our follow-up data. However, the increased activation in DD is located in typical regions of the fronto-parietal number network.

Interestingly, we did not find group differences at the baseline assessment. According to the literature significant differences are mainly reported in parietal, frontal and subcortical regions (e.g. (Kaufmann et al., 2009; Kucian, Loenneker, et al., 2011; Price et al., 2007). There are several reasons for this. Firstly, it seems that younger children with DD recruit more distributed brain regions and show higher inter-individual variability (Kucian et al., 2006). Consequently, it is statistically more difficult to find a common activation pattern in DD compared to TD children. A second reason is the rather strict significance level we have chosen to report our results. At a lower statistical threshold activation differences similar to those of Kucian et al. (2011) can be detected.

2.6.2 Typical and atypical development

Consistent with our expectations, TD children show a growing proficiency in number processing with development, as seen in a significant improvement in the number line task from 1 to 100. Still, DD children do not stagnate in their development, exhibiting a decrease in error when placing numbers on a number line. In fact, our results show that the dyscalculic’s number line performance improved more over time than that of the TD children. This result is consistent with other findings of long-term studies (Geary et al., 2012; Landerl, 2013). However, even when the gap between the typical and atypical development in the mental number line decreases, children with DD always performed significantly lower than their peers. As Shalev et al. (1998, 2005) stated in earlier studies, our results confirm that number representation in DD is deficient and delayed in development. In addition, children with DD still showed substantial deficits in simple arithmetic through the entire study. This result supports the importance of well working number processing abilities in order to develop arithmetical skills (Booth & Siegler, 2008).

The brain activation patterns of TD children revealed no significant difference over the examined time period. This result seems surprising given our hypothesis of an increase of activation in number-specific parietal regions and a decrease in domain-general regions, and is not consistent with the results from an earlier study, showing age related changes in the IPS during non-symbolic magnitude processing (Ansari & Dhital, 2006). However, it is important to note that most of the studies compare numeracy-established adults with developing children and therefore assume linearity in development. It might therefore be that some of the mentioned changes occur only at specific periods in development. In fact, there is little knowledge about the trajectory of neuronal development in number processing. Furthermore, previous studies looking at development investigated non-symbolic number processing or numerical distance effects (Ansari & Dhital, 2006; Ansari et al., 2005; Cantlon et al., 2006; Kaufmann et al., 2008; Kucian et al., 2008), while our task focussed on spatial number representation. On the other hand, the brain activation pattern from our results is in line with results from studies using a similar and the same task respectively (Fulbright, Manson, Skudlarski, Lacadie, & Gore, 2003; Kucian, Grond, et al., 2011). Moreover, our results are consistent with Kucian et al. (2008), revealing no differences comparing children over a 3-year period, but finding changes between children and adults. Along with the increasing proficiency on the behavioural level of number processing our results speak for a consistent and well working number processing network in TD children. However, our results do not exclude the notion that the number processing network continuously develops and refines in typical development over time.

Interestingly, children with DD show a remarkable activation increase in the entire fronto-parietal network over the observed period of development. The growth of activation in the bilateral insula and bilateral inferior frontal gyri is in good agreement with the literature, showing that these regions are known to play a crucial role in processes supporting working memory, attention and cognitive control. Together with the better performance in the fMRI task this finding supports the notion that children with DD constantly use domain-general regions to a larger extent, probably reflects higher cognitive demands and emotional control processes induced by the task. Additionally, children with DD showed an activation increase in the bilateral IPS during developmental time. This result is promising, providing further evidence that deviant parietal activity patterns are present in DD and that this region is associated with magnitude processing. In context with the improvement in the fMRI paradigm and the catch-up in the number line task, our results lend support to a stronger use of number-specific areas in children with DD. The negative interaction between group and time also revealed activation in parietal number-specific regions and frontal domain-general regions, indicating that the developmental changes were more pronounced in children with DD. This mirrors the results from our behavioural data and previous studies, showing that the gap between TD and DD performance diminishes during development (Geary et al., 2012; Landerl, 2013).

To our knowledge, no neuro-imaging long-term studies exist in the field of dyscalculia, but results from studies with dyslexic children also show differences in the development of the neuronal reading system. Comparable to our findings, in dyslexic children age related increases are seen in domain-specific occipito-temporal regions but also in domain-general regions (left IFG) (Shaywitz et al., 2007). Furthermore, Rosenberg-Lee and colleagues (2011) looked at brain maturation processes between 2nd and 3rd grades during arithmetic problem solving. In line with our results, better performance in arithmetic problem solving and a significant increase in activity were observed in the right superior parietal lobe, IPS and AG, PHG and frontal regions from 2nd to 3rd grade. Similarly, children's neuronal responses in bilateral IFG and IPS increased over a one-year period with improved numerical skills (Emerson & Cantlon, 2014). Based on these activation increases, which have been associated with initial stages of learning, the developmental effects in our DD group might also reflect neuronal maturation processes.

Taken together, our results support the notion that TD children have a consistent and functioning number processing network between 8 and 11 years, and therefore show few developmental effects over the time period examined. Dyscalculic children, however, show age-related changes in the frontal areas of the brain, which can be related to compensatory mechanisms or different but less effective task solving strategies, which are often observed in children with DD. Secondly, the increase in the domain-specific parietal areas hints to maturation or delayed development of number processing areas. Although these findings are promising, it is important to note that children with DD do not fully catch up to their peer group in numerical-arithmetical skills and show less focused activation patterns, underscoring that the deficiencies do not vanish with time.

2.6.3 Methodological considerations

To our knowledge this is the first longitudinal study looking at neuronal development in children with and without dyscalculia. The lack of other longitudinal studies in DD might arise from several reasons. Firstly, longitudinal fMRI studies in children are especially prone to high drop-out due to more movement artefacts and braces. This was also the case in our study and the reason why we have unequal and small sample sizes. For this reason, our results should be interpreted with caution. However, the same main results were obtained when evaluating the study with equal group sizes revealing that our results are stable and not based on differences in group size. Secondly, the choice of the fMRI paradigm, especially in longitudinal studies, is constrained by the requirements that it must be feasible for children with DD (performance over chance level) and not too easy for TD children (ceiling effects). An adaptation of the difficulty level of the task results in a loss of comparability over time, which we wanted to avoid. As a consequence, ceiling effects might have led to a loss of behavioural group differences at the second assessment point. Thirdly, longitudinal study designs are very time consuming regarding (re-)recruitment and maintenance of the participant’s motivation. Thus, developmental questions are in many cases examined by more time-efficient methods such as cross-sectional designs. Importantly, cross-sectional designs do not take into account inter-individual differences to the same extent as longitudinal designs. Furthermore, most cross sectional-studies compare adults and children and might therefore miss an opportunity to capture the full developmental trajectory. We think that our results are promising and provide an important contribution to the understanding of the typical and atypical development of number processing, but further work is needed to verify our findings and strengthen the understanding of developmental trajectories.

Despite these methodological considerations, our results shed light on the behavioural and neuronal trajectories in dyscalculia and emphasise the importance of longitudinal studies for the understanding of development. This knowledge contributes to the understanding of becoming numerate and might therefore be meaningful for education and further used for the implementation of therapy and support of children with difficulties in mathematics.

3 Do adolescents with developmental dyscalculia have a generalised magnitude deficit? Processing of discrete and continuous magnitudes

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To be submitted to Cortex, January 2015

3.1 Abstract

The link between number and space has been discussed in the literature for some time, resulting in the theory that number, space and time might be part of a generalised magnitude system located in the parietal lobe (ATOM-Theory). To date, several behavioural and neuroimaging findings support the notion of a generalised magnitude system, although contradictory results speaking for a partial overlap or separate magnitude systems are also found. The possible existence of a generalised magnitude processing area consequently leads to the question how children with developmental dyscalculia, known for their deficit in numerical-arithmetical abilities, process magnitudes. By means of neuropsychological tests and functional magnetic resonance imaging (fMRI) we therefore aimed to examine the relationship between number and space in typical as well as atypical development.

Participants were 16 adolescents with developmental dyscalculia (14.1 years) and 14 age-matched typically developing peers (13.8 years). In the fMRI paradigm participants were asked to perform discrete and continuous magnitude comparisons as well as a mental rotation task.

In the behavioural tests dyscalculic adolescents performed significantly worse in the numerical and more complex visuo-spatial tasks, but showed similar results when making simple magnitude decisions. A conjunction analysis of the imaging data revealed commonly activated higher order visual (inferior and middle occipital gyrus) and parietal magnitude (inferior and superior parietal lobe) areas over all three tasks. In addition, no differences were found when contrasting both tasks containing a magnitude decision, favouring the notion of a generalised magnitude system. Group comparisons further revealed that subjects with developmental dyscalculia showed increased activation in the left inferior frontal lobe, known to support domain general regions, whilst typically developing peers activate task specific areas to a greater extend.

In conclusion, our results point to the existence of a generalised magnitude system in the occipito-parietal stream. Moreover, adolescents with developmental dyscalculia seem to have preserved abilities to process discrete and continuous magnitudes. However, neuroimaging findings hint towards the use of compensatory mechanisms in dyscalculic subjects revealing a possible delay in the development of the magnitude system.

3.2 Introduction

The role of space in numerical processing has been discussed since the very beginning of the numerical and arithmetical scientific history. Galton's investigation about the spatial orientation of numbers revealed that subjects had internal representations with various visuo-spatial properties (Galton, 1880). Further empirical evidence led to the conclusion that our representation of numbers is organised from left to right according increasing size, nowadays referred to as the mental number line (Dehaene, 1992). Extensively studied psychophysical effects such as the distance effect (subjects are more accurate and faster when comparing numbers that are far apart) (e.g. Moyer & Landauer, 1967) and the SNARC-effect (Spatial Numerical Association of Response Codes; subjects respond faster to small numbers with the left hand and to large numbers with the right hand than vice versa) (e.g. Dehaene, Bossini, & Giraux, 1993; Schweiter, Weinhold Zulauf, & von Aster, 2005) demonstrate the link to the spatial aspect of numerical processing. Size effects were also found for dot patterns, brightness, or length showing that the interaction between space and number also applies for non-symbolic and continuous magnitudes (Buckley & Gillman, 1974; Moyer & Landauer, 1967). With the background of the previous reported empirical evidence, Walsh (2003) goes one step further and proposes in A Theory Of Magnitude (ATOM) that time, space and quantity are part of a generalised magnitude system, rather than being analysed and compared in separate systems. He further argues that the magnitude system is located in the parietal lobe and evolved from processing visual input in its spatial and temporal dimensions in order to produce action-directed motor output (Bueti & Walsh, 2009; Walsh, 2003). This is in line with knowledge from the last decades of imaging studies showing that numerical magnitude processing is conducted mainly in the intraparietal sulcus and adjacent regions (e.g. Dehaene et al., 2003; Kaufmann et al., 2013).

Further evidence for the ATOM theory is found in animal studies. Tudusciuc and Nieder (2007, 2009) showed in single-cell experiments with monkeys that continuous (e.g. length) and discrete magnitudes (e.g. arrays of dots) are both processed by shared (fronto-)parietal areas. The underlying visuo-spatial magnitude judgement for length works similarly in monkeys and humans (Tudusciuc & Nieder, 2010). In 9-month-old infants a transfer effect across magnitude dimensions of space, number and time could be measured in associative learning providing support for an innate aspect of the general magnitude system (Lourenco & Longo, 2010). In addition, visuo-spatial abilities are widely reported to be one of the main predictors for later mathematical skills (Assel, Landry, Swank, Smith, & Steelman, 2003; Mazzocco & Thompson, 2005; Verdine, Irwin, Golinkoff, & Hirsh-Pasek, 2014).

In adults several behavioural studies report that different magnitude dimensions influence each other. Hurewitz et al. (2006) showed that judgments of numerosity, size, or area of dots resulted in a bidirectional interference between the discrete and continuous dimensions of the stimuli. Similarly, numerosity and length both affected the processing of time (Dormal & Pesenti, 2012). However, there have also been reports finding contradictory results. For instance, no correlation among estimations of time, space and numerosities was found in the study of Agrillo et al. (2013).

Results from fMRI studies revealed an activation overlap in the IPS irrespective of the processed magnitude (size/ luminance/ numbers (Pinel, Piazza, Le Bihan, & Dehaene, 2004), angles/ lines/ numbers (Fias et al., 2003), luminance/ number line (Vogel, Grabner, Schneider, Siegler, & Ansari, 2013)). In addition, repetitive transcranial magnetic stimulation (rTMS) over the right IPS induced increased error rates in a length as well as in a numerosity estimation task (Dormal, Andres, et al., 2012). In line with these findings, numerosity training coupled with transcranial random noise stimulation (tRNS) led to better and longer lasting improvements in the precision of the approximate number sense (Cappelletti, Gessaroli, et al., 2013). Interestingly, transfer effects to quantity judgements in a time and space task could be found supporting the theory of a shared cognitive and neuronal mechanism (Cappelletti, Gessaroli, et al., 2013).

In summary, behavioural and neuroimaging studies offer a broad variety of hints about the relationship of space and number. Several findings support the theory of a generalised magnitude system, although contradictory results speaking for a partial overlap or separate magnitude systems are also found (Cappelletti, Chamberlain, et al., 2013).

In the context of the previous presented evidence and the possibility for a generalised magnitude system, it would be interesting to examine magnitude processing and its visuo-spatial influence in subjects with specific deficits in number processing, as it is the case in DD. This disorder is defined as a specific learning disability affecting the acquisition of basic numerical-arithmetical skills that is not explicable on the basis of general mental retardation or of inadequate schooling (WHO, 2010). DD has a prevalence of about 3-7% (Gross-Tsur et al., 1996; Wyschkon et al., 2009) and a persisting character (Shalev et al., 1998, 2005) which might further result in behavioural-emotional problems (Auerbach et al., 2008) and reduced employment opportunities (Parsons & Bynner, 2005). Children with DD show a variety of numerical deficits such as counting, magnitude processing, spatial number representation and fact retrieval (Geary, 1993; Landerl, 2013; Landerl et al., 2004; Mussolin, Mejias, et al., 2010; Rousselle & Noël, 2007); for an overview see Kucian and von Aster (2014). In addition, domain-general factors such as spatial working memory, executive functions and visuo-spatial abilities (Ashkenazi et al., 2013; Cowan & Powell, 2014; Fias et al., 2013; Rotzer et al., 2009; Skagerlund & Träff, 2014; von Aster & Shalev, 2007) are discussed in the literature to contribute to the clinical picture of DD.

Regarding the visuo-spatial deficits, several behavioural studies investigated the relationship between number and space in children with DD. The study of Rourke and Finlayson (1978) was one of the first to point out that children with DD often have difficulties solving tasks with spatial aspects (e.g. Object Assebly, Block Design of the WISC). They further argue that, "specific deficiencies in arithmetic calculation skills are due to difficulties in visuo-spatial organization and integration" (Rourke & Finlayson, 1978, p. 130). In a study about the cognitive profiles of dyscalculia, children showed besides the known deficits in symbolic and non-symbolic magnitude processing, lower values in the visuo-spatial subtest Block Design of the WISC (Landerl et al., 2009). In contrast, no differences were found in the comparison of physical sizes of numbers (e.g. 2 6) (Landerl et al., 2004, 2009). Osmon and co-authors (2006), found in math-impaired adults that spatial skills, measured with the Judgment of Line Orientation task, differed from math-unimpaired subjects. Spatial abilities were further found to relate to math achievement after removing general intellectual variance. Similarly, children with DD showed significantly lower performances in all three magnitude-processing abilities proposed by the ATOM theory (number, space, and time) pointing to a deficit in general magnitude processing (Skagerlund & Träff, 2014). On the other hand, Szucs et al. (2013) did not find differences in spatial abilities of dyscalculic children of the same age range. According to their conclusion, deficits in short-term and working memory account for the often reported difficulties in visuo-spatial abilities.

To our knowledge, only one neuroimaging study looked at numerical and spatial abilities in children with DD (Kaufmann et al., 2009). The subjects had either to take a decision about the number of fingers shown or the orientation of the palms. In the spatial condition, children with DD produced significantly stronger activation in the right postcentral gyrus/IPS than TD children. Moreover, significant group differences in beta weights could be found in the right inferior parietal lobe (IPL) for the space condition, whilst the number condition produced differences in the left IPL. Kaufmann et al. (2009) concluded that the stronger activation in task relevant regions reflects compensatory mechanism needed in children with DD.

To date, several behavioural studies point to deficiencies in visuo-spatial abilities in dyscalculic children (Landerl et al., 2009; Rourke & Finlayson, 1978; Skagerlund & Träff, 2014). Furthermore differences in the right IPL but not left IPL could be detected in a neuro-imaging study with dyscalculic children for a spatial task (Kaufmann et al., 2009). This contributes to the idea of a shared magnitude system in the right parietal lobe. Hence, not only a deficit in number processing but in the general magnitude system might underlie the mechanisms of DD. However, there are only few studies looking at the relationship of space and number systematically, despite the manifold nature of spatial abilities. Correspondingly, the conducted studies to date have measured simple (e.g. length estimation) as well as complex visuo-spatial abilities (e.g. mental rotation tasks). These tasks involve higher cognitive functions to a different degree and are therefore difficult to compare.

3.3 Aim and hypotheses

The main goal in our study was, to evaluate the theory of a generalised magnitude system looking at various visuo-spatial abilities by means of behavioural as well as neuroimaging measures. We aimed to develop a fMRI task that measures discrete quantity processing (non-symbolic numerosity comparison), continuous quantity/visuo-spatial processing (angles comparison) and complex visuo-spatial processing (mental rotation). The second research question intends to examine if there are behavioural and neuronal differences in adolescents with and without DD regarding the generalised magnitude processing.

Based on the previous literature, we hypothesise that the numerical as well as the visuo-spatial task containing a magnitude judgement activates a core region for magnitude processing in the IPS (Fias et al., 2003; Pinel et al., 2004; Vogel et al., 2013; Walsh, 2003). We predict to find similar behavioural performance and no brain activation differences between these two conditions in TD adolescents. Secondly, we expect to find deficiencies in behavioural visuo-spatial as well as numerical performance in dyscalculic adolescents (Skagerlund & Träff, 2014). In line with Kaufmann et al. (2009) aberrant activation of parietal regions is predicted for adolescents with DD. The finding of intact magnitude processing in TD subjects and a deficit performance in DD subject would point to the existence of a generalised magnitude system.

3.4 Methods

3.4.1 Participants

Twenty adolescents with DD and 17 TD adolescents between 11.6 and 16.5 years were recruited into this study. Inclusion criteria for all participants were no history of neurological or psychiatric diseases and an IQ above 85, measured by the fourth edition of the WISC (Similarities, Block Design, Matrix Reasoning) (Petermann & Petermann, 2007). Furthermore, the mathematical performance of adolescents with DD had to be under the cut-off of the standardised numerical test battery Basic Diagnosis in Mathematics Education for Grades 4-8 (BASIS-MATH 4-8) (Moser Opitz et al., 2010). TD adolescents had to perform on an age-appropriated level. According to these criteria, three participants were excluded from the study. For the fMRI analysis, additional four subjects were excluded because of movement artefacts or scanner problems. Hence, subsequent analyses are based on 16 adolescents with DD (14.1 years) and 14 TD adolescents (13.8 years). Groups were matched for age, gender, handedness and pubertal status as determined by the Edinburgh Handedness Inventory (Oldfield, 1971) and an adapted version of the Self-administered Rating Scale for Pubertal Development (Carskadon & Acebo, 1993) respectively (Table 3.1). Informed consent was obtained from participants when 16 years of age or older and all parents. The study was approved by the local ethics committee based on guidelines from the World Medical Association’s Declaration of Helsinki (WMA, 2002).

3.4.2 Neuropsychological testing

Numerical achievement

Numerical achievement was assessed using the Basic Diagnosis in Mathematics Education for Grades 4-8 (BASIS-MATH 4-8) (Moser Opitz et al., 2010), which is the only German test available up to eighth grade to identify numerical deficiencies. The test battery measures various numerical abilities at three difficulty levels such as counting, arithmetic, decimal system, text problems and part-whole-relationships. Criteria for DD are met if the performance falls under a threshold value of 67 points (out of a total of 83 points). This is interpreted as not reaching mastery of basic mathematical concepts.

Additionally, the subtest Quantity Comparison of the Cognitive Abilities Test (KFT 4-8+R) (Heller & Perleth, 2000) was used as a curricular test to assess the subjects' mathematical performance at a peer level. Adolescents had 10 minutes time to solve as many problems as possible of increasing difficulty. Note that for this subtest data could not be collected for all participants (3 DD missing, 6 TD missing) and must therefore be interpreted cautiously.

Visuo-spatial abilities

Because of the multifarious nature of visuo-spatial abilities, the tasks are subdivided into visuo-perceptive, visuo-cognitive and visuo-constructive tasks (Kerkhoff, 2006).

Firstly, visuo-perceptive abilities include amongst others the perception of position in space, length, and distance discrimination (Kerkhoff, 2006). Based on the Birmingham Object Recognition Battery (BORB) (Riddoch & Humphreys, 1993) three computerised subtest were programmed on E-prime (Version 2, Psychology Software Tolls Inc., USA) to assess length, size, and position estimation. In the length estimation task subjects had to decide which of two simultaneously presented lines was longer. Correspondingly, in the size task two presented dots had to be compared regarding their diameter. Both tasks consisted of 30 items and had three difficulty levels with the ratios of 0.75 (simple), 0.85 (medium), or 0.95 (difficult). In the position estimation task, subjects had to match the position of gaps in two circles and indicate if they are at the same or at different positions. Sixty items were shown, whereby simple items differed by 12°, medium by 8°, and difficult by 4°. All tasks were self-paced and responses were given by the keys q (for left is bigger) and p (for right is bigger) or the mouse buttons (index finger for "yes", middle finger for "no"). Correct responses were balanced for left and right or "same" and "different" respectively.

Secondly, visuo-cognitive abilities include in addition to the mere perception of visual stimuli an operation in space, such as mental rotation or change of perspective (Kerkhoff, 2006). In the Form Constancy task of the Developmental Test of Visual Perception - Adolescent and Adult (DTVP-A) (Reynolds, Pearson, & Voress, 2002), subjects were shown a stimulus figure and asked to find it twice in a series of figures. The targeted figure appeared in a different size, position and/or shade, and could be hidden in a distracting background. Secondly, subjects solved the Paper Folding subtest of the KFT 4-8+R (Heller & Perleth, 2000). In this task a square sheet of paper was folded 1 to 4 times and then perforated. Subjects had 8 minutes to indicate for as many items as possible how the paper would look when unfolded.

Lastly, visuo-constructive skills indicate the ability to combine elements to a whole, such as drawing a geometrical figure or assembling cubes to one figure (Kerkhoff, 2006). In the Copying subtest of the DTVP-A (Reynolds et al., 2002), individuals were shown a simple figure and asked to draw it. Subsequent figures were increasingly complex, eventually becoming three-dimensional. Additionally, the Block Design subtest of the WISC-IV (Petermann & Petermann, 2007) was performed, where subjects had to build a figure with cubes according to a model.

Reading abilities

The 1-Minute-Reading-Task from the Salzburg Reading and Orthography Test (Moll & Landerl, 2010) assessing word and pseudoword reading fluency was used to estimate the reading performance and control for dyslexia. Because of lacking test norms in grades 7 and 8, values were obtained by interpolating the norms from the test manual (grade 6) and from Kronschnabel et al., (2013) (grade 9).

Working memory

In order to control for memory effects verbal memory span and working memory was assessed using the subtest Digit Span of the WISC-IV (Petermann & Petermann, 2007). In this task subjects had to repeat an auditorily presented sequence of numerals forwards and backwards respectively. Visuo-spatial working memory was measured with the suppression-task of the

Block-Tapping-Test (Beblo et al., 2004; Schellig, 1997). The task required subjects to reproduce every second block of a previous presented sequence on a board with nine cubes.

Attention

Levels of attention and inhibition were measured by means of the subtests Alertness and Go-nogo of the Testbattery for Attentional Performance (TAP) (Zimmermann & Fimm, 1993). In the Alertness subtest, subjects had to react as quickly as possible to a target stimulus (intrinsic alertness) which was sometimes preceded by a cue stimulus (phasic arousal). In the Go-nogo subtest, subjects had to react as quickly as possible to a target stimulus (go condition), but inhibit reactions on a second presented stimulus (nogo condition).

Behavioural data analysis

Behavioural data was statistically analysed with SPSS (Version 20). To assess group differences parametric t-tests for independent samples or non-parametric Kolmogorov-Smirnov-Z-test were performed if the assumption of normality was violated.

3.4.3 Brain imaging

fMRI paradigm

The fMRI paradigm was newly designed for this study and intends to measure perceptive and cognitive spatial as well as magnitude processing. In the task a green and a blue Pacman with varying arrays of dots, mouth size, and rotation angles were presented simultaneously (Figure 3.1). In the first experimental condition (numerical condition), participants had to compare the dot arrays and indicate which Pacman holds more dots in his belly. This non-symbolic magnitude comparison task requests a decision about a discrete quantity. Secondly, the perceptive spatial condition asked which Pacman's mouth was bigger, requiring a visuo-perceptive and continuous magnitude decision. Thirdly, in the mental rotation condition adolescents were asked to judge if the Pacmen would face towards each other if rotated to an upright position. This task intends to measure visuo-spatial ability, which is not intertwined with a magnitude decision. Additionally, it involves more higher order cognitive functions (executive functions), thereby representing a more complex spatial task than the perceptive spatial condition. Finally, the control task is a simple colour discrimination task including no judgement of magnitude or visuo-spatial abilities. In order to avoid strong engagement of executive functions, needed if switching between several tasks, a blocked design was chosen rather than an event-related design. Additionally, we wanted to optimise the signal in terms of high pass filtering (see also Henson, 2007), which led us to design a paradigm with three runs. Each run lasted 6min 10s and consisted of four blocks of one of the experimental conditions alternating with four blocks of the control condition. Order of runs and blocks were

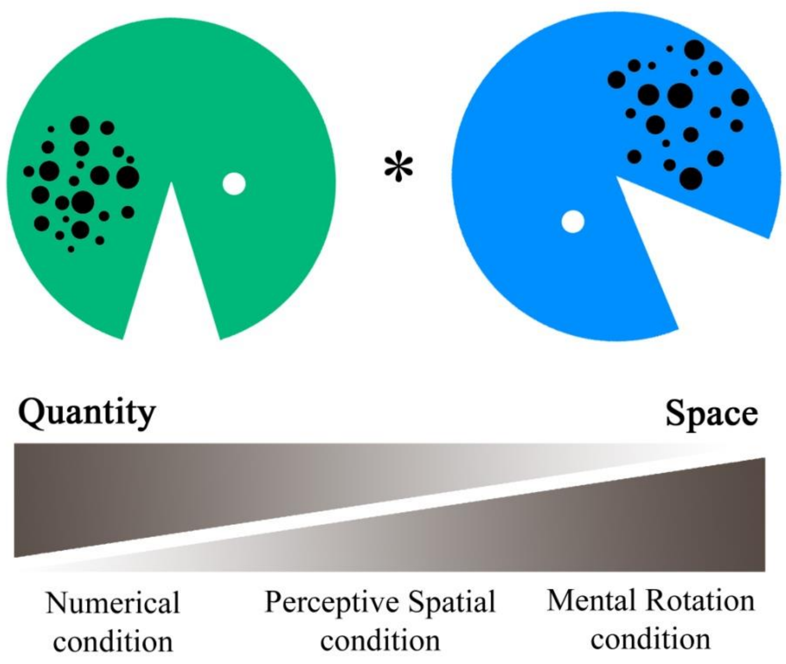

Figure 3.1 In the fMRI paradigm a green and a blue Pacman with varying arrays of dots, mouth size, and rotation angles were presented simultaneously. In the numerical condition participants had to indicate which Pacman holds more dots, requesting a decision about discrete quantity. Secondly, in the perceptive spatial condition participants had to indicate which mouth was bigger, requesting a continuous magnitude and spatial decision. Thirdly, in the mental rotation condition participants were asked if the Pacmen would face towards each other when rotating to an upright position, requesting mainly a spatial decision. Finally, in the control condition subjects had to indicate which Pacman was green.

counter-balanced between subjects. At the beginning of each block an instruction was shown for 3s, followed by a blank screen of 500ms and a block of the experimental or control condition lasting for 30s. Between the blocks a 13s rest period with a fixation cross was presented, resulting in a total block length of 46.5s. The paradigm was self-paced. Nonetheless stimuli were displayed maximally for 2.5s with an inter-trial-interval jittered between 1300 and 4300ms (M = 2500ms).

A single stimulus consisted of a Pacman with a diameter of 13.2cm created in Adobe Photoshop (Version 5, Adobe Systems Inc.). The dot arrays were controlled for dot size, total surface and density. Dots varied between 0.25 and 1cm in diameter, had a total surface of 590cm^2 and were either spread on a small (5x6cm) or al large area (6x7cm) (see also Gebuis & Reynvoet, 2012). Dot arrays contained between 14 and 28 dots, representing three ratios of varying difficulty (array to be compared to = 20 dots, simple: ratio = 0.70, 14 or 28 dots; medium: 0.83, 17 or 24 dots; and difficult: 0.91, 18 or 22 dots). Similarly, for the comparison of the mouth angles three difficulty levels were set according to the ratio of the angles (angle to be compared to = 45°, simple: ratio = 0.76, 34° or 59°; medium: 0.93, 41.5° or 48°; and difficult: 0.97, 43° or 46°). In the mental rotation task 135° (simple), 180° (medium) or 225° (difficult) of total rotation had to be completed. Items were set at six different starting positions (45°, 90°, 135°, 225°, 270°, and 315°) relative to the upright position (0°). Finally, colours for the control task were of the same luminance to avoid any comparative processing of brightness (see also Pinel et al., 2004). The ratios of this task were set carefully based on a pilot behavioural study with 60 children (mean age 12.9 years) and a subsequently testing phase in the scanner (adults) (for results see Grond, Kucian, O'Gorman, Martin, & von Aster, 2012). Critically, as the stimuli were exactly the same over all four tasks, conditions are highly comparable in terms of visual input, eye movements and motor responses. The stimuli were presented in pairs horizontally aligned via a video goggles system (VisuaStimDigital, Resonance Technology Inc., USA). The distance from the screen was therefore the same for all subjects (30° in the horizontal visual field of view). The subjects answered by a button press of the dominant hand (index finger for "yes" or "left", middle finger for "no" or "right"), which was recorded using an MRI compatible response box (Lumina Respond Pad, Cedrus

Corporation, USA). The paradigm was programmed on E-Prime (Version 2, Psychology Software Tolls Inc., USA), taking into account that stimuli were pseudo-randomised and correct answers balanced for left/right.

Image acquisition

MRI data were acquired on a 3T General Electric Discovery 750 Scanner (GE Medical Systems, USA) using an 8-channel head coil. Whole brain functional images were acquired sequentially with a gradient echo EPI sequence (38 slices, 3mm slice thickness (ST), 0.3mm interslice skip, 64x64 matrix size (MS), field of view (FOV) = 240mm, flip angle (FA) = 74°, echo time (TE) = 32ms, repetition time (TR) = 1900ms). Additionally, a T1-weighted structural image was obtained with a spoiled gradient echo sequence (3D SPGR, ST = 1mm, no interslice skip, MS = 256x256, FOV = 256mm, FA = 8°, TE = 5ms, TR = 11ms).

Participants were carefully instructed and supplied with hearing protection before entering the scanner. To minimise head motion, the head was stabilised with padding.

fMRI preprocessing

The fMRI data were analysed by means of Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for NeuroImaging, UK) running under Matlab (Release 2012b, The MathWorks Inc., USA).

Three dummy scans, acquired to stabilise magnetisation at the beginning of the scan, were excluded from the analysis. Afterwards, the subjects' functional scans were realigned with rigid body transformations using the mean image as a reference scan. Six motion parameters (translation in x, y, and z direction as well as rotation in pitch, roll and yaw) were stored and included later in the analysis to control for motion. The mean functional image was then coregistered to the subjects' T1-weighted anatomical scan. In a next step, the individual anatomical scan was segmented into grey (GM) and white matter (WM) according to tissue probability maps of a paediatric atlas (NIH Paediatric Database) (Fonov et al., 2011, 2009). The paediatric atlas, created for the ages 4.5 to 18.5

years, was chosen due to obtaining better segmentation results than with the adult template. Parameters from the coregistration and segmentation were then applied to the functional scans to normalise images into MNI space. Finally, the functional images were smoothed with a Gaussian kernel of 6mm FWHM (full width half maximum).

fMRI statistics

The first level analysis was performed using a mass-univariate approach based on the GLM (General Linear Model). The time series from each subject were modelled with an event related design for the experimental and control condition using a canonical HRF (hemodynamic response function). The six subjects' motion parameters were entered as additional regressors. Slow signal drifts and serial correlations were accounted for by using a high-pass filter of 128s and a first level autoregressive model during maximum-likelihood estimation of the GLM parameters.

At the second level, a full factorial analysis with the factors group (DD, TD) and task (numerical, perceptive spatial, mental rotation) was conducted for the contrast images experimental-control condition.

Statistical results are shown with a threshold of $p < .05$ family-wise error (FWE) correction and minimum cluster size of $k \geq 5$ voxels. Alternatively results are presented with a less strict significance level of $p < .001$, corrected for multiple comparisons using a cluster-extent threshold of $k \geq 23$ voxels ($621mm^3$). According to Slotnick (2008), the spatial autocorrelation of the data was estimated. Then a Monte Carlo simulation was run with 10'000 iterations, using a type I error voxel activation probability of .001, and an estimated FWHM as a Gaussian smoothing kernel in order to derive the cluster extent threshold yielding the desired correction for multiple comparisons at a $p < .05$ level (Slotnick, 2004).

Anatomical localisation of the fMRI results was attained through the SPM Anatomy Toolbox v2.0 (Eickhoff et al., 2005, 2007) and is reported in the MNI coordinate space.

3.5 Results

3.5.1 Behavioural data

The neuropsychological results and the demographic data for all participants are summarised in Table 3.1. All participants reached normal range of intelligence in the WISC-IV (DD IQ = 92-117, TD IQ = 97-122). However, group differences could be detected in the estimated general IQ and the single subtests (Table 3.1). Differences in IQ scores between a group of children with learning disabilities and a control group are often reported in the literature (Geary et al., 2000; Landerl, 2013; Willcutt et al., 2013). One reason for this is that IQ tests are not independent from numerical skills. Furthermore, the fact that we did not have artificially matched IQ groups, allowed us to include all DD subjects, resulting in a sample that represents the clinical population of persons with DD well. Importantly, none of our DD adolescents performed below an IQ of 92, meeting the criteria according to the ICD-10 (WHO, 2010) and DSM-V (IQ > 70, ± 5 point measurement error) (American Psychiatric Association, 2013). The IQ was not entered as a covariate in the subsequent behavioural and fMRI analysis, since IQ is not independent from the effects of interest (Dennis et al., 2009; Field, 2009; Miller & Chapman, 2001).

Regarding the comorbid disorders ADD/ADHD, dyslexia and working memory deficits, groups did not differ significantly in any measurement of attention, reading or memory performance (all $p \geq .21$, Table 3.1).

Numerical achievement

Numerical abilities, assessed by the Basis-Math, differed highly between the TD and the DD group ($p < .001$) (Table 3.1). Importantly, looking at the three difficulty levels of the Basis-Math tests revealed that subjects with DD performed consistently worse in all difficulty levels, showing deficits even in very basic arithmetical skills (level 1: $t(16.4) = -5.76$, $p < .001$, level 2: $t(23.2) = -6.15$, $p < .001$, level 3: $t(28) = -6.69$, $p < .001$). Similarly, the groups differed in the curricular test Quantity Comparison (KFT 4-8R+), with the DD subjects scoring significantly lower than the matched TD group ($p < .01$).

Visuo-spatial abilities

In the visuo-perceptive tasks, accuracy was measured by calculating the ratio of the correctly solved items compared to the total number of items. The results revealed that both groups were able to solve the length and size estimation task well. The position estimation task was more difficult for the adolescents as seen by the lower accuracy values. All participants solved the task with an accuracy level of over 50%, except for 2 DD and 2 TD subjects. However, no significant differences could be found between the groups in any of the visuo-perceptive tasks (all $p \geq .05$) (Table 3.1). Regarding the measured RT, both groups solved the task with a similar velocity (length estimation: $t(17.9) = 0.85$, $p = .408$), size estimation: $t(26) = 0.77$, $p = .449$), position estimation: $t(26) = -0.40$, $p = .696$).

In the visuo-cognitive abilities, significant differences between groups could be found in both tests. Adolescents with DD performed worse than the TD adolescents in the Form Constancy subtest of the DTVP-A ($p < .05$). The DD group also scored significantly lower in the Paper Folding subtest of the KFT 4-8R+ than the TD group ($p < .01$) (Table 3.1).

Finally, in the visuo-constructive tasks, no difference could be found in the Copying subtest of the DTVP-A. Although, a clear tendency for differences in performance can be detected, with dyscalculic adolescents reaching a mean PR of 40, whereby TD adolescents score at PR 59 ($p = .07$). In the Block Design subtest of the WISC-IV, subjects with DD performed constantly lower than TD subjects ($p < .01$) (Table 3.1).

Table 3.1 Demographic characteristics and scores of numerical abilities, visuo-spatial abilities, domain general cognitive abilities, memory, attention and reading.

Measure	Dyscalculic children N=16		Typically developing children N=14		Test-statistics	p-value
	M	SD	M	SD		
Age	14.1	1.2	13.8	1.3	0.705[a]	0.487
Gender m/f	4/12		4/10		0.049[b]	1.000
Handedness l/a/r	2/2/12		1/4/9		1.367[b]	0.515
Pubertal status	2.8	0.8	2.8	0.7	0.610[c]	0.737
Numerical abilities						
BASIS-MATH 4-8	50.8	11.3	75.1	4.2	-7.971[a]	<0.001
KFT 4-8+R Quantity Comparison	40.2	4.6	53.6	4.9	-6.395[a]	<0.001
Visuo-spatial abilities						
Length estimation (accuracy)	91.9	7.6	92.2	6.0	0.567[c]	0.715
Size estimation (accuracy)	98.4	2.1	97.4	3.1	0.567[c]	0.596
Position estimation (accuracy)	63.0	10.8	65.0	11.0	-0.485[a]	0.632
KFT 4-8+R Paper folding	40.4	10.5	52.4	9.0	-3.234[a]	0.003
DTVP-A Form Constancy	71.3	21.7	83.6	14.8	1.415[c]	0.014
DTVP-A Copying	40.0	25.2	58.8	29.3	-1.887[a]	0.070
Domain general cognitive abilities (WISC-IV)						
Block Design	97.2	14.8	112.5	12.1	-3.075[a]	0.005
Similarities	103.8	7.6	112.1	4.7	-3.562[a]	0.001
Matrix Reasoning	100.6	8.5	113.2	11.7	-3.395[a]	0.002
Estimated general IQ	100.5	6.5	112.6	5.7	-5.421[a]	<0.001
Memory (BTT, WISC-IV)						
Visuo-spatial working memory	6.0	1.8	7.1	1.9	0.833[c]	0.235
Verbal memory span	5.6	1.3	5.7	1.2	-0.335[a]	0.740
Verbal working memory	4.4	1.1	5.1	1.3	0.659[c]	0.407
Attention (TAP)						
Alertness	48.8	21.5	52.0	15.3	-0.457[a]	0.651
Go-nogo	40.1	16.1	40.1	15.0	0.659[c]	0.668
Reading (SLRT-II)						
Words					15.088[b]	0.213
Pseudowords					15.088[b]	0.326

BASIS-MATH 4-8 = Basic Diagnostic in Mathematics Education for Grades 4-8,
KFT 4-8+R = Cognitive Abilities Test [T-score], DTVP-A = Developmental Test of Visual Perception - Adolescent and Adult [PR], WISC = Wechsler Intelligence Scale for Children [IQ-Score], BTT = Block-Tapping-Test, TAP = Testbattery for Attentional Performance [PR], SLRT-II = Salzburg Reading and Orthography Test
[a] t-Test, [b] Fisher’s Exact Test, [c] Kolmogorov-Smirnov-Z Test

Behavioural results from fMRI task

As the fMRI paradigm was newly designed for this study and adolescents solved it in a self-paced mode, we firstly looked at some general features of the paradigm before looking at group differences. Hence, the number of solved items was quantified and entered into a mixed-model analysis of variance (ANOVA) with experimental condition as a within-subject factor and group as a between-subject factor. Results showed a significant effect of condition ($F(1.5, 41.5) = 7.65$, $p = .004$) and no effect of group ($F(1, 28) = 0.004$, $p = .950$) or interaction ($F(1.5, 41.5) = 0.12$, $p = .831$). Post-hoc t-tests revealed that more items were solved in the numerical condition ($M = 72.5$, $SD = 3.2$) compared to the perceptive spatial condition ($M = 70.4$, $SD = 3.3$) ($t(29) = 5.75$, $p < .001$).

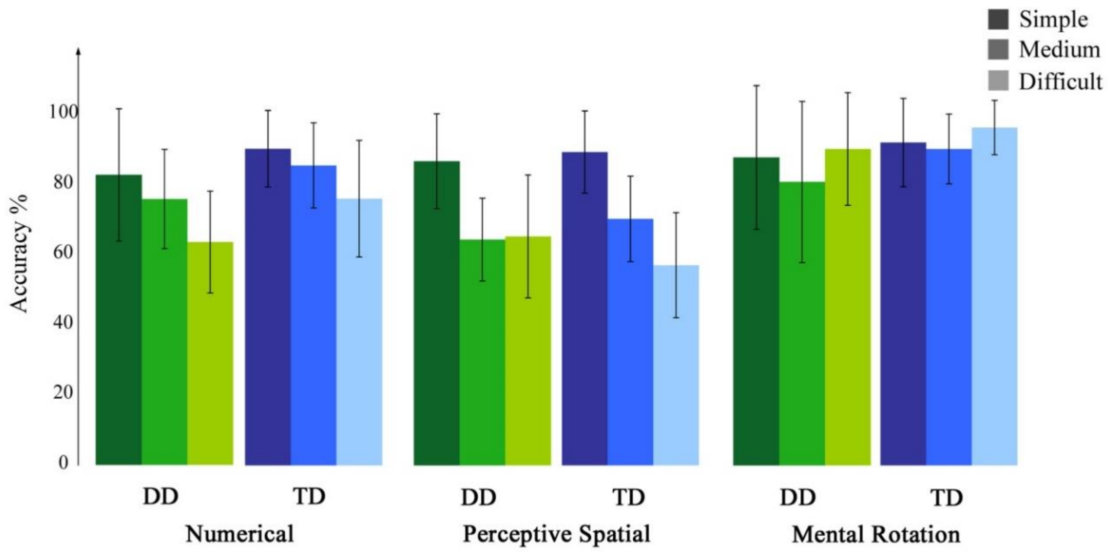

Figure 3.2 Behavioural results (accuracies) of the fMRI paradigm for each experimental condition split up for the three difficulty levels, the lighter the colours the more difficult the tasks.

Accuracy and RT were calculated for each single condition, excluding trials in which RT was smaller than 300ms and misses. For the control condition a single value was calculated over the three runs. Correct and incorrect trials were included in the subsequent analysis. All participants performed in every condition above chance level (50%). Regarding accuracy, an ANOVA with experimental condition and difficulty level as a within-subject factors and group as a between-subject factor revealed significant effects of condition ($F(2, 56) = 24.32$, $p < .001$) and difficulty ($F(2, 56) = 24.51$, $p < .001$). Furthermore, the interaction condition by difficulty level reached significance ($F(4,28) = 16.06$, $p < .001$). No effect of group or further interaction was significant (all $p \geq .07$). Post-hoc t-test showed that the DD group solved significantly fewer items correctly in the difficult level of the numerical condition compared to the TD group ($t(28) = -2.22$, $p = .035$) (Figure 3.2). Furthermore, the analysis of the RT revealed no differences in any condition between groups (all $p \geq .66$).

Motion determined by the total displacement of the motion fingerprint (Wilke, 2012) was not significantly different between runs, experimental conditions or groups (all $p \leq .14$).

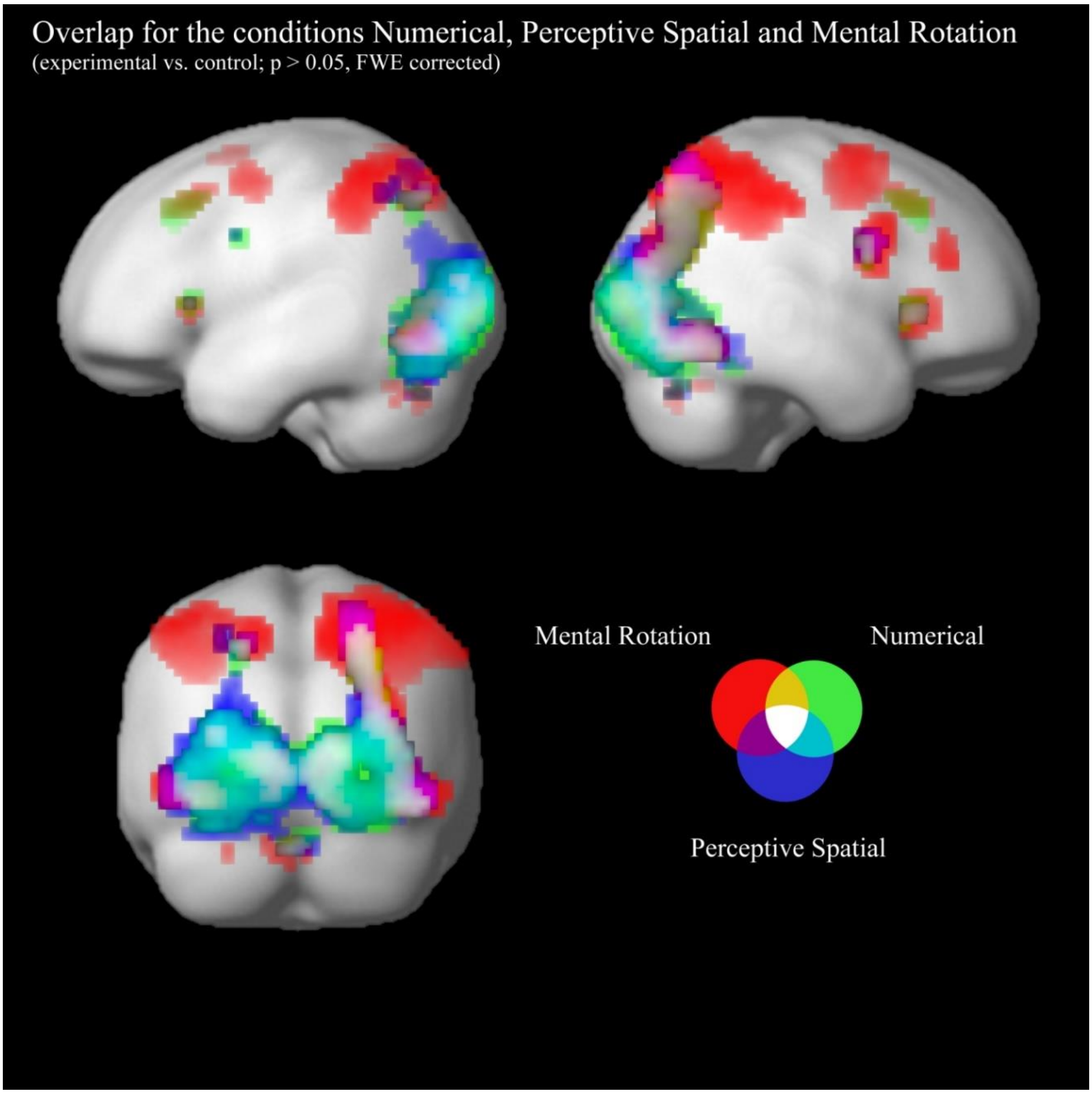

Figure 3.3 Brain activation of the experimental conditions: numerical (green), perceptive spatial (blue), and mental rotation (red). Overlap between the magnitude conditions (numerical and perceptive spatial) is shown in turquoise, between the space conditions (perceptive spatial and mental rotation) in violet, and between the mental rotation and the numerical condition in yellow. Commonly activated regions in all three experimental tasks appear in white. Note that the overlap corresponds to the results of the conjunction analyses.

Table 3.2 Brain areas that showed significant activation in the conjunction analyses for all experimental conditions, magnitude conditions and visuo-spatial conditions respectively ($p < .05$, $k \geq 5$, FWE corrected).

Region	**Cluster size**	**Peak t-value**	**Peak MNI coordinates**		
			x	**y**	**z**
Conjunction analyses					
Numerical, Perceptive Spatial and Mental Rotation (experimental conditions)					
R middle occipital gyrus	249	6.59	28	-71	33
R inferior occipital gyrus (assigned to fusiform gyrus)		6.57	43	-65	-12
R calcarine gyrus (assigned to V1)	144	7.79	13	-86	6
N/A (assigned to V1)	119	6.80	-14	-86	3
L inferior occipital gyrus	38	6.34	-35	-77	-9
R insula lobe	10	5.27	34	22	3
L superior parietal lobe (assigned to area 7A)	6	5.21	-20	-71	48
L middle occipital gyrus	6	5.42	-29	-89	15
Numerical, Perceptive Spatial (magnitude conditions)					
L middle occipital gyrus	1850	9.60	-29	-89	15
R middle occipital gyrus		8.03	31	-86	15
R calcarine gyrus (assigned to V1)		7.79	13	-86	6
R insula lobe	10	5.27	34	22	3
L superior parietal lobe (assigned to area 7A)	9	5.21	-20	-71	48
Cerebellar vermis	7	5.22	4	-71	-27
Perceptive Spatial, Mental Rotation (visuo-spatial conditions)					
R inferior temporal gyrus (assigned to fusiform gyrus)	402	7.24	46	-68	-12
R superior parietal lobe (assigned to area 7A)		6.74	22	-68	57
R calcarine gyrus (assigned to V1)	147	8.09	13	-89	6
N/A (assigned to V1)	119	6.80	-14	-86	3
L inferior occipital gyrus	87	6.34	-35	-77	-9
R precentral gyrus	31	5.90	49	4	30
L superior parietal lobe (assigned to area 7A)	12	5.21	-20	-71	48
R insula lobe	10	5.27	34	22	3
L inferior parietal lobe (assigned to intraparietal sulcus)	8	5.06	-29	-56	48
L middle occipital gyrus	6	5.42	-29	-86	15

3.5.2 fMRI

fMRI task effects

Firstly, conjunction analyses were conducted over both groups to examine jointly used regions over all experimental conditions (FWE corrected at $p < .05$) (Figure 3.3, Table 3.2). A conjunction analysis of the three experimental tasks over both groups activated mainly regions in the bilateral middle (MOG) and inferior occipital gyrus (IOG) extending into the right inferior and superior parietal lobe (SPL) (see white coloured areas of Figure 3.3 and Supplementary Figure 1 in Appendix B). Further activation could be found in the right calcarine gyrus, right insula lobe and the left SPL. If conducting a conjunction analysis only with the tasks containing a magnitude decision (numerical condition and perceptive spatial condition), a similar pattern could be detected (turquoise and white coloured areas of Figure 3.3 and Supplementary Figure 2 in Appendix B). However, the activation in the visual areas (MOG, IOG) is pronounced to a much larger extent and additional activation in the cerebellum (vermis) is found. The activation pattern for the conjunction analysis only with the tasks containing a spatial decision (perceptive spatial condition and mental rotation condition) revealed solely an additional activation in the right precentral gyrus (violet and white coloured areas of Figure 3.3 and Supplementary Figure 3 in Appendix B).

Secondly, comparisons between the conditions were conducted to examine regions used specifically for the single conditions (Figure 3.4, Table 3.3). In contrast to the conjunction analysis only data from the TD group was used in this analysis in order to avoid any influence of the DD group on the results. Several regions survived FWE correction, but results are reported with a $p < .001$ significance level as described before.

Numerical versus perceptive spatial: The contrast numerical versus perceptive spatial condition revealed no significant differences.

Perceptive spatial versus numerical: The contrast perceptive spatial versus numerical condition revealed no significant differences.

Mental rotation versus numerical: The mental rotation task elicited greater activation compared to the numerical task in the right IPS, the right MOG reaching into IPL, left IPL and the right superior frontal gyrus (SFG) (Figure 3.4 A).

Numerical versus mental rotation: The opposite contrast revealed higher activation in the bilateral IOG/MOG, bilateral insula lobe, left superior medial (SMdG) and SFG (Figure 3.4 B).

Mental rotation versus perceptive spatial: For the mental rotation task activation increase was found in the right IPS (extending into the angular gyrus), the supramarginal gyrus, the MOG, and bilateral SFG/SMdG compared to the perceptive spatial task (Figure 3.4 C).

Perceptive spatial versus mental rotation: The perceptive spatial condition however revealed higher activation in the left MOG, the medial temporal gyrus (MTG) and the SFG (Figure 3.4 D).

fMRI group differences

In the numerical condition, adolescents with DD showed increased activation in the left IFG compared to TD adolescents (Figure 3.5 A, Table 3.4). TD subjects did not elicit higher activation in any regions compared to dyscalculic subjects in the numerical task.

In the perceptive spatial condition dyscalculic adolescents showed increased activation in the left IFG, whereas TD adolescents had higher activation in the left MOG (Figure 3.5 B and C, Table 3.4).

Finally, in the mental rotation task neither the DD nor the TD adolescents showed activation differences when comparing them against each other.

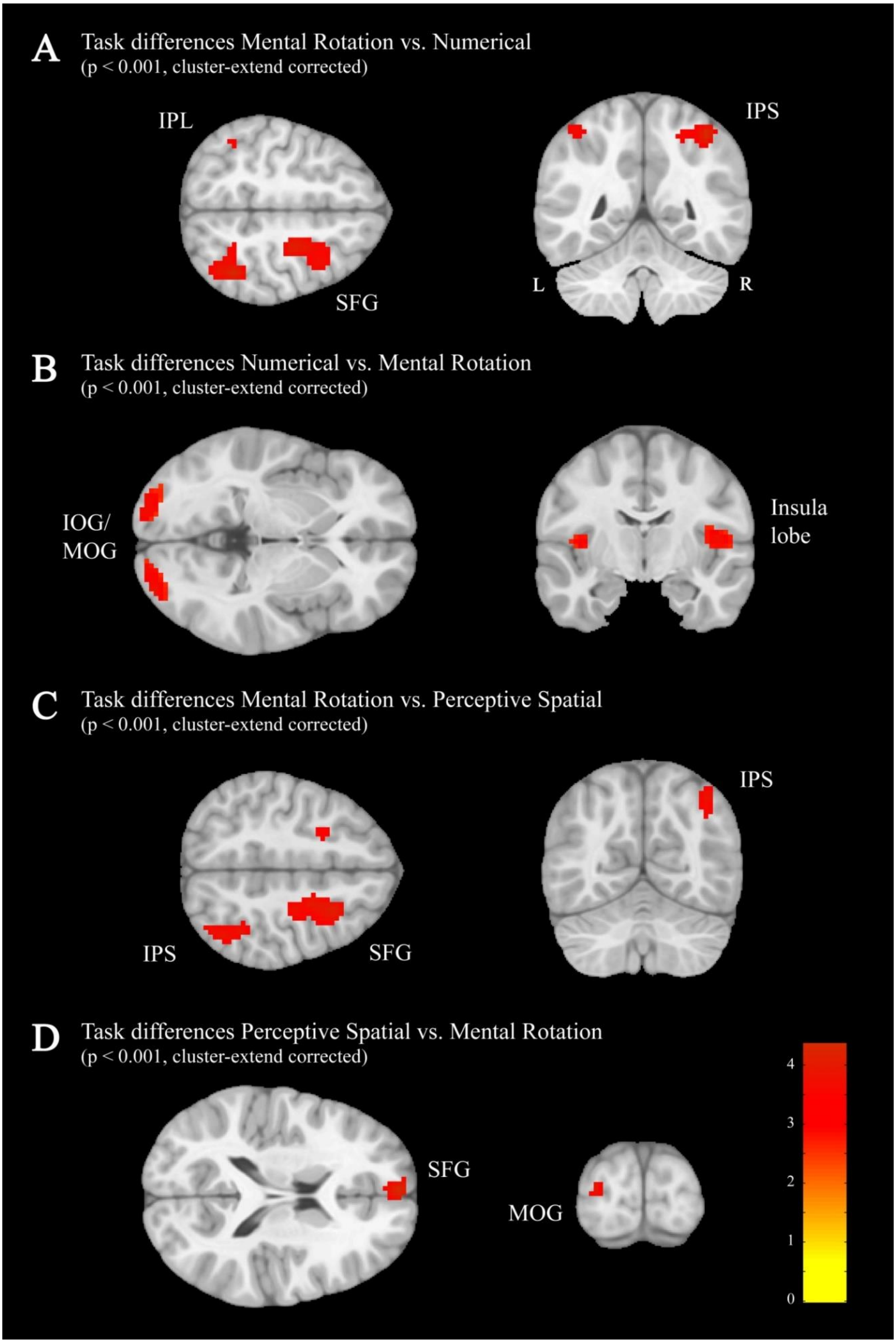
A
Task differences Mental Rotation vs. Numerical
(p < 0.001, cluster-extend corrected)
IPL
SFG
IPS
L
R
B
Task differences Numerical vs. Mental Rotation
(p < 0.001, cluster-extend corrected)
IOG/
MOG
Insula
lobe
C
Task differences Mental Rotation vs. Perceptive Spatial
(p < 0.001, cluster-extend corrected)
IPS
SFG
IPS
D
Task differences Perceptive Spatial vs. Mental Rotation
(p < 0.001, cluster-extend corrected)
SFG
MOG
4
3
2
1
0

Figure 3.4 Task differences for typically developing adolescents shown on a paediatric template (Fonov et al., 2009) with a significance level of $p < 0.001$, cluster extend corrected. (A) Increased activation for the mental rotation versus numerical condition. (B) Increased activation for the numerical versus mental rotation condition. (C) Increased activation for the mental rotation versus perceptive spatial condition. (D) Increased activation for the perceptive spatial versus mental rotation condition. IOG: inferior occipital gyrus, IPL: inferior parietal lobe, IPS: intraparietal sulcus, MOG: middle occipital gyrus, SFG: superior frontal gyrus.

Table 3.3 Brain areas that showed significant activation for the different task comparisons in typically developing adolescents ($p<.001$, $k \geq 23$, cluster-extend corrected).

Region	**Cluster size**	**Peak t-value**	**Peak MNI coordinates**		
			x	**y**	**z**
Task effects					
Numerical > Perceptive Spatial					
n.s.					
Perceptive Spatial > Numerical					
n.s.					
Mental Rotation > Numerical					
N/A	301	4.33	31	1	45
R superior frontal gyrus		4.29	25	-8	60
R inferior parietal lobe (assigned to intraparietal sulcus)	217	4.70	40	-50	54
R superior parietal lobe (assigned to intraparietal sulcus)		3.94	28	-56	63
R middle occipital gyrus	29	3.87	40	-74	30
L inferior parietal lobe	28	4.27	-44	-56	60
Numerical > Mental Rotation					
L superior parietal gyrus (assigned to fusiform gyrus)	215	4.87	-14	64	21
L superior medial gyrus		4.07	-2	61	18
R inferior occipital gyrus (assigned to V3)	213	6.05	22	-92	-6
R middle occipital gyrus		5.22	31	-92	3
R Insula/ Rolandic operculum	129	5.13	49	-5	9
L calcarine gyrus	129	5.03	-17	-98	-3
L insula lobe	36	4.32	-41	-11	9
Mental Rotation > Perceptive Spatial					
R superior frontal gyrus	405	4.79	22	1	66
R middle frontal gyrus		4.52	25	10	45
R inferior parietal lobe (assigned to intraparietal sulcus)	146	4.05	40	-50	54
L middle frontal gyrus	44	3.71	-26	-2	54
R supramariganl gyrus (assigned to inferior parietal lobe)	40	3.96	58	-29	45
R middle occipital gyrus	26	4.44	40	-71	30
Perceptive Spatial > Numerical					
L superior frontal gyrus (assigned to fusiform gyrus)	119	4.43	-5	61	18
L middle occipital gyrus (assigned to V3)	27	3.76	-29	-95	12
L middle temporal gyrus	24	4.49	-62	-35	0

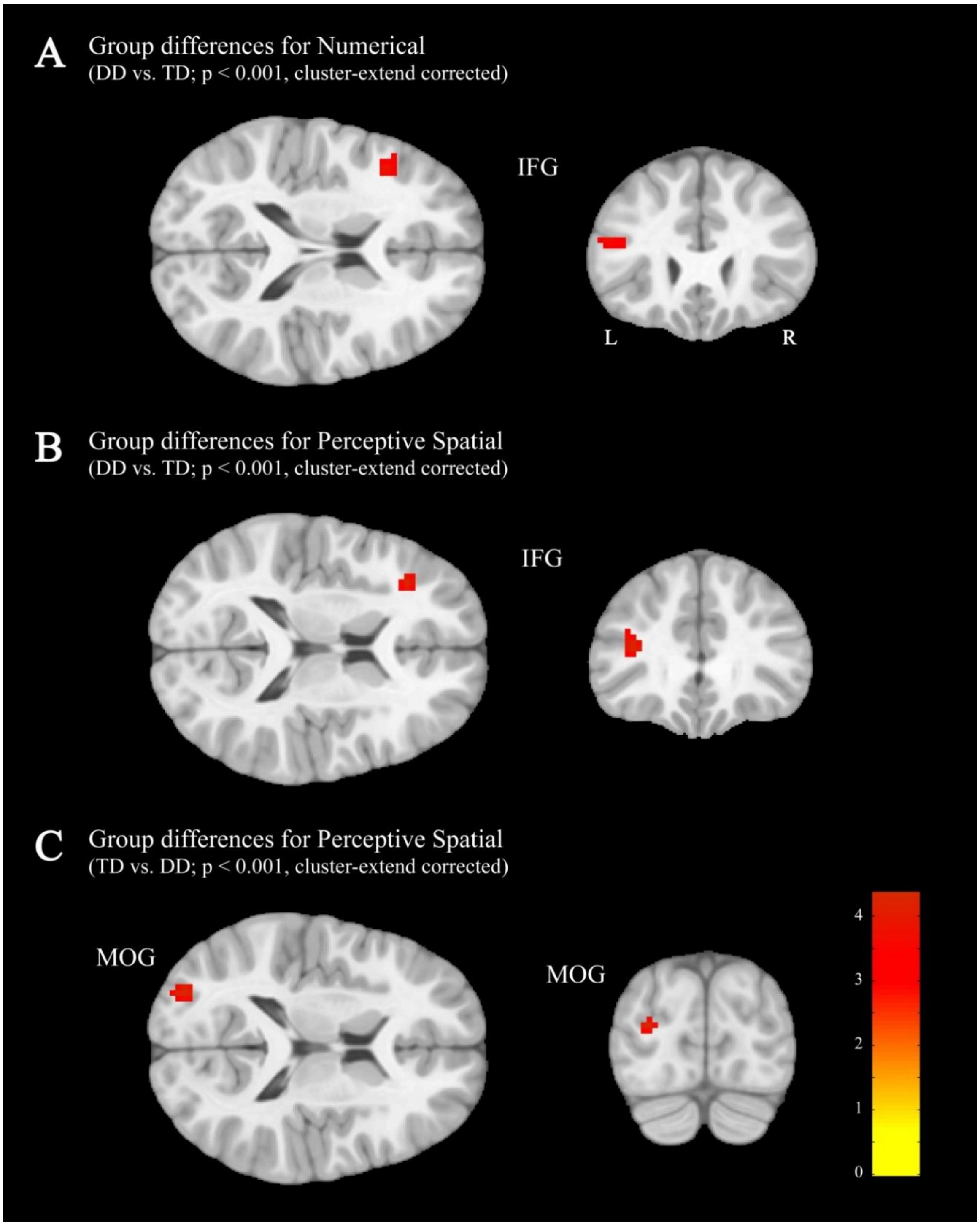

Figure 3.5 Group differences shown on a paediatric template (Fonov et al., 2009) with a significance level of $p < 0.001$, cluster extend corrected. (A) Increased activation in the dyscalculic adolescents compared to the typically developing group for the numerical condition. (B) Increased activation in the adolescents with developmental dyscalculia compared to the typically developing peers for the perceptive spatial condition. (C) Increased activation in typically developing adolescents compared to dyscalculic adolescents for the perceptive spatial condition. IFG: inferior frontal gyrus, MOG: middle occipital gyrus.

Table 3.4 Brain areas that showed significant activation in the different conditions when contrasting DD adolescents and TD adolescents ($p<.001$, $k\geq 23$, cluster-extend corrected).

Region	**Cluster size**	**Peak t-value**	**Peak MNI coordinates**		
			x	**y**	**z**
Group effects					
Numerical DD>TD					
L inferior frontal gyrus	37	4.26	-41	19	21
Numerical TD>DD					
n.s.					
Perceptive Spatial DD>TD					
L inferior frontal gyrus	27	4.35	-35	31	15
Perceptive Spatial TD>DD					
L middle occipital gyrus	24	4.12	-29	-86	15
Mental Rotation DD>TD					
n.s.					
Mental Rotation TD>DD					
n.s.					

3.6 Discussion

The link between space and number has been discussed and investigated in the literature for some time, leading to the theory that time, space, and number might be part of a generalised magnitude system located in the parietal cortex (Walsh, 2003). In the present study, we therefore examined the relationship of space and number by means of behavioural and neuroimaging methods. The fact that we studied this relationship in TD adolescents as well as in adolescents with number processing deficits (DD) enabled us to investigate the mechanisms of the generalised magnitude system in more detail. In conjunction analyses we found an overlap in the higher order visual areas and parietal magnitude processing areas after taking into account all experimental tasks. The tasks containing magnitude decisions elicited an almost identical neuronal network revealing no significant differences when contrasting them. On the other hand, tasks containing spatial decisions differed in their activation map with the mental rotation task activating more right parietal and frontal regions and the perceptive spatial task activating mainly higher order visual areas. Regarding the second research question, adolescents with DD showed beside the numerical difficulties an additional deficit in cognitive and constructive visuo-spatial abilities in the behavioural tests. Brain imaging results further revealed that DD adolescents engage more domain-general frontal regions when solving magnitude tasks, whilst TD adolescents activate task-specific areas to a higher extent.

3.6.1 A generalised magnitude system in the occipito-parietal lobe

The main goal of this study was to elaborate the theory of a generalised magnitude system looking at various visuo-spatial abilities. In our fMRI task we therefore aimed to measure discrete quantity processing (numerical condition), continuous quantity/visuo-spatial processing (perceptive spatial condition) and complex visuo-spatial processing not asking explicitly for a magnitude decision (mental rotation). Because the fMRI task was used for the first time in this study, we initially checked if the task was feasible for both groups and if the set levels were perceived as increasing difficult. In all three conditions subjects solved in average between 70 and 72 items and groups did not differ in the number of solved items. We therefore conclude that the tasks are comparable between conditions and groups. Furthermore, with increasing difficulty level the accuracy decreases constantly in the numerical as well as in the perceptive spatial condition, showing that we succeeded in creating three difficulty levels in both magnitude processing conditions (Figure 3.2). Although difficulty levels were set according to previous behavioural tests (Grond et al., 2012), subjects perceived the continuous (perceptive spatial) condition as more difficult than the discrete (numerical) condition, which was also shown in the literature (Leibovich & Henik, 2013a). In the mental rotation condition, however, accuracy was similar for all difficulty levels (Figure 3.2). This might be explained by different strategies used to solve the task.

An important point to address in the context of non-symbolic number processing is the finding that numerosity is not processed independently from its continuous visual variables (diameter, total surface, density) (Gebuis & Reynvoet, 2012). We controlled the continuous visual properties for our non-symbolic trials by first varying the size of dots in its diameter within the single items, second keeping the total surface constant between items, and third spreading the dots on a big or small area independent of their numerosity. Consequently, subjects were forced to solve the task by mainly a numerical decision. Our fMRI paradigm met the aim to measure discrete and continuous magnitude processing as well as visuo-spatial processing. The task was feasible for the subjects in the chosen age range and comparable between groups.

The first research question aimed to evaluate the theory of a generalised magnitude system in the parietal lobe. As hypothesised, the conducted conjunction analysis over all three experimental tasks revealed activation especially in the right IPL and SPL (Figure 3.3). This is in line with the prediction of a generalised magnitude system in the parietal lobe (Walsh, 2003) and with several studies looking at different modalities of magnitude. A study with numerosity and length processing elicited activation in the bilateral IPS (IPL/SPL) in a conjunction analysis (Dormal & Pesenti, 2009). The right IPS and posterior SPL were found to be commonly involved when performing number line and brightness estimations (Vogel et al., 2013). Finally, the study of Pinel et al. (2004) looking at number, size and luminance comparisons revealed activation in bilateral anterior IPS. This is in agreement with the findings of brain stimulation studies showing that disrupting the right IPS led to increased error rates in numerosity and length estimation (Dormal, Andres, et al., 2012). On the other hand, stimulation of the right parietal lobe improved numerosity but also quantity judgements in time and space (Cappelletti, Gessaroli, et al., 2013).

Our results also revealed clusters of activation in the bilateral higher order visual areas MOG/IOG as well as in the primary visual cortex (V1). This was not the case in the aforementioned studies (Dormal & Pesenti, 2009; Vogel et al., 2013). However, Kaufmann et al. (2008) also looked at mental rotation and non-symbolic numerosity, reporting activation in the same areas. Similar to our study, they also used colour discrimination as the control task. The observed activation in the occipital lobe might therefore be due to the mental rotation task, using additional and different visual processing areas. Alternatively, the variety of control tasks used could explain the inconsistent findings in the occipital regions. As expected, a conjunction analysis over the three runs of the control task revealed activation in the primary visual areas (V2/BA 18) and the ventral extrastriate cortex (V3) known to process colour. Because we used the contrasts experimental versus control for the group analysis, visual areas not used for colour processing appear as a result (IOG assigned to the fusiform gyrus, V4, MOG, and calcarine gyrus/V1).

Finally, activation in areas of the frontal brain (precentral and postcentral gyrus, supplementary motor area, dorsolateral prefrontal cortex and medial frontal gyrus (MFG)) is often reported in magnitude comparisons, which was not the case in our study (Dormal, Dormal, et al., 2012; Dormal & Pesenti, 2009; Kaufmann et al., 2008; Pinel et al., 2004; Vogel et al., 2013). A reason for this might be the rather different spatial tasks we used involving executive functions to a different degree.

In the conjunction analysis with the tasks explicitly asking for magnitude decisions, an almost identical network was detected (Figure 3.3). Moreover, the task-specific comparisons between the perceptive spatial and the numerical condition did not lead to any significant differences. These findings argue for a common used network irrespective of a discrete or continuous magnitude judgment, in agreement with several studies (Agrillo et al., 2011; Dormal & Pesenti, 2009; Fias et al., 2003; Hurewitz et al., 2006; Tudusciuc & Nieder, 2007, 2009) and the proposed magnitude theory of Walsh (2003). Furthermore, additional activation in the occipital lobe was found including broad parts of the visual areas (IOG/MOG: V1, V2, V3 and V4). Roggeman et al. (2011) disentangled in an adaptation study differed stages of non-symbolic quantity processing. When looking at large versus small processed numerosities they obtained similar activations in the bilateral MOG (Roggeman et al., 2011). In other words, it seems that a rough estimation of quantity is already performed in the occipital lobe. Our results might extend these findings by showing that not only numerosities but also continuous magnitudes are processed in this approximate occipito-parietal stream. Moreover, the mental rotation task, which did not require any magnitude estimation, did not induce occipital activation to the same extent.

The conjunction analysis of the spatial tasks elicited, in addition to the commonly used regions of all three tasks, activation in the right precentral gyrus (Figure 3.3). Activation in this region is widely discussed in mental rotation studies and has been associated with motor simulation and motor planning/ execution (Zacks, 2007), which might also be of use in taking decisions about a continuous spatial dimensions.

Not surprisingly, task specific differences between the mental rotation task and the perceptive spatial or numerical tasks were found in similar regions, namely right IPS, right MOG, and right/bilateral SFG. These regions are known to be involved in visuo-spatial image transformations, working memory and monitoring (Arsalidou & Taylor, 2011; Fias et al., 2013; Zacks, 2007). The opposite contrasts (numerical versus mental rotation, perceptive spatial versus mental rotation) revealed in both cases activation in the frontal pole of the left MFG and SFG, which has been associated with goal directed behaviour (Arsalidou & Taylor, 2011). Furthermore, activation in the IOG and MOG differed in terms of location, reflecting the diverse parts of the visual areas that are essential to process the different visual stimuli as discrete dot patterns and continuous angles. In the numerical condition bilateral insula activation was found. This region has been implicated in switching between working memory and default states during problem solving (Arsalidou & Taylor, 2011).

Taken together, differences in task specific activation is mainly explained by the extent to which domain-general functions are involved in the single conditions. On the other hand, similar activation patterns in the parietal lobe were observed indicating a comparable involvement of the domain-specific areas. Hence, our first research question would clearly support the notion of a generalised magnitude system.

3.6.2 Preserved spatial-perceptive abilities in DD

In our second research question, we intended to investigate differences regarding the general magnitude system in adolescents with and without dyscalculia. If a shared magnitude system exists, it would be reasonable to find additional visuo-spatial deficits in adolescents with DD taking into account their deficits in numerical processing. Alternatively, dissociation of these two functions could possibly argue for partially overlapping or even separate systems. Our DD group performed significantly worse than the control group in all numerical tasks, showing difficulties in basic arithmetical skills. According to our hypothesis, we further found significantly lower performances in a variety of behavioural visuo-spatial tasks. More precisely, DD participants performed significantly worse in the visuo-cognitive and visuo-constructive tasks, but reached similar levels in all visuo-perceptive tasks compared to the TD group. Several other studies have also reported deficits in visuo-spatial abilities in DD, although most of them examined only one of the various spatial components (Osmon et al., 2006; Rourke & Finlayson, 1978; Skagerlund & Träff, 2014). However, the observed deficits to date mostly rely on visuo-cognitive and visuo-constructive tasks (block design, judgement of line orientation, paper folding, and mental rotation), which is in line with our results. This is supported by the finding, that continuous quantity processing performances in adults with DD seem to be preserved (Cappelletti, Chamberlain, et al., 2013). On the other hand, accuracies in our behavioural length and size estimation task are near to ceiling and might not disclose subtle differences between the groups. This seems unlikely, as no differences in the position estimation task and the perceptive spatial condition of the fMRI task could be found.

In the fMRI paradigm, the only significant behavioural difference was found in the most difficult level of the numerical task. Previous findings about non-symbolic magnitude processing are inconclusive (Castro Cañizares et al., 2012; Kucian, Loenneker, et al., 2011; Landerl, 2013; Mussolin, Mejias, et al., 2010; Piazza et al., 2010; Price et al., 2007). In addition, the extent to which continuous properties of the dot patterns were controlled differs, limiting the comparability of the studies. Regarding our data, we may conclude, that adolescents with DD are able to perform discrete non-symbolic comparisons, but show more errors with increasing difficulty of the task compared to TD peers.

Regarding brain activation, only tasks containing magnitude decisions elicited neuronal differences between groups (Figure 3.4). In both tasks, subjects with DD showed increased activation in the left IFG, an area known to be important for monitoring items or simple rules (Arsalidou & Taylor, 2011). This might suggest that dyscalculic participants rely more on domain-general abilities to solve the task, as reported often in the literature (e.g. Kaufmann et al., 2011; Kucian, Loenneker, et al., 2011). In contrast, TD adolescents produced stronger activation in the left MOG, part of the dorsal extrastriate cortex, when processing continuous magnitudes using more task-specific regions to solve the task. Interestingly, no differences in the parietal lobe were found between groups, even when lowering the significance threshold to $p < .005$. On the one hand, this could reflect that adolescents with DD process simple numerosities and magnitudes in the same way as their peers. On the other hand, the more inferior areas of the occipital lobe might play a more important role in the approximate processing of numerosities than assumed. In fact, group differences were found in the MOG (MNI: x = -29, y = -86, z = 15) which has also been reported to be involved in rough estimations of quantity in the study of Roggeman et al. (2011) (MNI: x = -25, y = -91 z = 3).

Our results point to a mostly well-functioning discrete and continuous magnitude processing in adolescents with DD. On the neuronal level, the increase in frontal activation might explain the use of compensating domain-general regions, revealing possible difficulties in dyscalculic adolescents. TD peers have increased activation in task relevant areas probably using a more efficient way of processing magnitudes. In this context, the deficits in number processing and arithmetic cannot be explained with a general magnitude deficit as proposed in previous studies (Noel & Rousselle, 2011; Rousselle & Noël, 2007). Furthermore, adolescents with DD only show visuo-spatial deficits in more complex tasks which involve executive functions to a greater extent. This better complies with the view that multiple neuro-cognitive components contribute to the explanation of DD (Fias et al., 2013). Alternatively, the significant IQ differences between the groups could partially explain the lower performance in higher order visuo-spatial tasks.

Leibovich and Henik (2013b) suggest a developmental model with regard to a generalised magnitude system, which is in agreement with the present results. They argue that from an evolutionary point of view a “quick and dirty” estimation is sufficient. The first stage in development is the innate ability to discriminate continuous magnitudes. This is followed by learning the relationship between discrete and continuous properties: larger area and density usually means more numerous. In a further stage, children are able to integrate discrete and continuous properties to discriminate magnitudes. Lastly, with formal education symbolic representations of numbers are learned, allowing the detection of exact differences between magnitudes (Leibovich & Henik, 2013b; see also von Aster & Shalev, 2007). According to our results, adolescents with DD seem to have accomplished the first three stages in the proposed developmental model, though showing somewhat difficulties to reach the last stage compared to TD adolescents. Further studies are needed looking into typical as well as atypical development to confirm our results. We also propose to test the ability to process continuous and discrete magnitudes in younger children with DD to find out if these abilities are maintained or deficient at a younger age.

In summary, adolescents with DD seem to have a preserved parietal magnitude system for discrete and continuous sizes favouring the proposed theory of a generalised magnitude system

(Walsh, 2003). Hence, to explain the additional difficulties in higher order visuo-spatial tasks and the substantial deficits in numerical and arithmetical skills more knowledge about the developmental trajectory of the magnitude system and the interactions with different cognitive domains is needed. In addition, a multiple-component view might rather be taken into consideration for the explanation of DD.

3.6.3 Limitations

In the present study some limitations regarding group differences, paradigm design and interpretation of the data have to be taken into account.

Firstly, the revealed differences in the estimated IQ between adolescents with and without dyscalculia might limit the interpretation of the results. However, IQ tests are known to be not completely independent from numerical skills, and differences in IQ measures between a group of children with learning disabilities and a control group are often reported (Geary et al., 2000; Landerl, 2013; Willcutt et al., 2013). All our participants were well matched for comorbid measures and reached IQ scores in normal range, clearly fulfilling the diagnostic criteria for DD. In this context, the fact that we did not find differences in discrete and continuous magnitude processing, despite IQ differences, actually strengthens our findings. Furthermore, structural studies report deficient fibre projection between parietal, temporal and frontal regions in children with DD (Kucian et al., 2013; Rykhlevskaia et al., 2009). Intact white matter projections linking frontal and parietal areas seem to be crucial for performance in general intelligence (Gläscher et al., 2010; Kucian, Kaufmann, & von Aster, 2014). This evidence could further explain why children with DD often score lower in IQ tests. In the context of the present arguments, we believe that our dyscalculic participants represent the clinical population better than a population selected or artificially matched for IQ.

Secondly, although carefully planned and developed, the paradigm did not control for eye movements. This is important to consider, as studies show that saccades activate bilateral areas of the SPL and parts of the IPS (Culham & Valyear, 2006; Simon et al., 2004; Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002). We accounted for this problem by presenting our paradigm via video goggles, thus controlling the distance from the subject to the screen. Furthermore, the horizontal visual field of view was only 30°, minimising eye movements to a small area. While presenting the same stimuli in all conditions, the subject had always to consider both items for a judgment of the task. We therefore assume that eye movements between conditions and subjects differ only slightly and do not affect the present results substantially. We propose for further studies to control eye movement by an eye tracking device.

Finally, in this study there is no neuroimaging data present to be able to compare directly between the non-symbolic magnitude system and symbolic number processing, which is important for arithmetic and found to be deficient in DD. It would be interesting to examine if the symbolic number processing avails itself of the areas found to be involved in the general magnitude system. This would provide important knowledge to the understanding of the cause and development of DD.

In conclusion, the results obtained in the present study, favour the possibility of a generalised magnitude system in the parietal lobe. It might be further assumed, that with development more refined and specific neuronal functions form in order to process magnitudes with increasing difficulty (Leibovich & Henik, 2013b). Secondly, despite the numerical deficits and difficulties in more complex spatial skills, adolescents with DD seem to have preserved abilities to process discrete and continuous magnitudes. Neuronal findings may reveal the use of compensatory systems, hinting to a slight delay in the development of the discrete and continuous numerical system. Further studies are needed to examine the development of the generalised magnitude system in typical and, more importantly, in atypical development.

4 General discussion

In the following general discussion, the results of the presented thesis are discussed with regard to the typical and atypical development of numerical representations and magnitudes. Following this, the role of space in the processing of numbers and the organisation of number and magnitude representations in the parietal lobe are addressed. Finally, future directions of the research conducted in the field of numerical cognition and certain problems related with the transfer of knowledge into practice are pointed out.

4.1 Typical development of magnitude and number representation

Described in a nutshell, the inborn capacity to process numbers approximately develops into a precise and spatially organised number representation through the acquisition of number words and number symbols. This tool further enables us to perform simple arithmetic operations, such as addition and multiplication, and later on to learn more complex mathematical procedures.

The presented data provides insight into the development of the spatially oriented number line and the acuity of the number representation. Over the examined time of 4 years, TD children showed improvements in the placement of numbers on a number line. In agreement with the literature and developmental models, our results reveal a constant increase in the acuity of number representation between the ages of 9 and 14 years (Kaufmann et al., 2011; Kucian & Kaufmann, 2009; Landerl, 2013; Siegler & Booth, 2004; von Aster & Shalev, 2007). To date, most of the studies investigated number acuity and the formation of the number line during the time children learn and establish the symbolic number system (ages 5 to 11 years) (Ebersbach et al., 2008; Landerl, 2013; Piazza et al., 2010; Siegler & Booth, 2004). The present finding extends this knowledge by showing that number representation continues to specialise long after the acquisition of number words and Arabic symbols. This is also reflected in the neuronal findings. Although no significant changes were present during development, a consistent but more focussed activation pattern was observed after 4 years in TD children. This is in agreement with the literature and hints to the possibility of underlying refinements during development (Durston et al., 2006; Karmiloff-Smith, 2010). As reviewed in the introduction, Arabic numbers are perceived automatically with their magnitude around the age of 9 years (van Galen & Reitsma, 2008). Furthermore, activation in the left IPS has been related to the growing acuity of number skills (Emerson & Cantlon, 2014). Accordingly, our results show that bilateral activation in the IPS and adjacent regions was present upon the first measurement point. It therefore supports the notion that number representation is already well established at the age of 9 years and shows few developmental effects over the examined time.

The results of the second study revealed that in adolescence, continuous and discrete magnitudes were both processed with high accuracy and almost identical neuronal networks. This favours the view, that continuous and discrete magnitudes might rely on one generalised system for magnitude as proposed by Walsh (2003). Regarding today's evidence that infants already have the ability to perceive numerosities and magnitudes, one could speculate that the inherited system for numerosity is also involved in continuous magnitudes processing (Izard et al., 2009; Lourenco & Longo, 2010). Alternatively, the ANS could be preceded by the ability to discriminate continuous magnitudes and the correlation between continuous and discrete properties may be learned later in development (Leibovich & Henik, 2013b). The present results show that, despite the increasing number acuity during development, the ability to process magnitudes is specialised in adolescents. This enables 14 year old to discriminate magnitudes with the ratio up to 0.97. The asymmetric activation pattern with stronger involvement of the right dorsal visual stream is compatible with the results from Roggeman et al. (2011), showing that a rough estimation of non-symbolic quantity is already performed in the occipital lobe.

In summary, the present findings comply with the developmental models proposing that number representations behaviourally and functionally specialise with age and experience. Our data further provides evidence that this ability is not restricted to number representations, but can be expanded to the processing of continuous dimensions. Furthermore, number acuity continues to develop during adolescence, in a time when number words and Arabic symbols are well mastered. Consequently, a more differentiated view ought to be incorporated in future developmental models proposing that number but also magnitude acuity develop over time. Our results further reflect that a more right occipito-parietal network is activated during the processing of discrete and continuous magnitudes, supporting the notion that the occipital lobe is already involved in a rough estimation of non-symbolic quantity.

4.2 Atypical development of magnitude and number representation

To date, the current body of research has identified a substantial deficit in numerical processing in children with DD. Despite the importance of those results, little is known about the neuronal development of this learning disability. It is therefore not clear if the improvements shown in behavioural long-term studies are only due to advanced compensation mechanisms or if number-specific areas also progress during development. The present thesis provides first insights on the neuronal developmental course of number and magnitude processing in DD.

In line with the literature, children with DD showed over the entire study phase difficulties in the processing of numbers and arithmetic (Geary et al., 2012; Kucian et al., 2006; Landerl, 2013; Mussolin, De Volder, et al., 2010; Piazza et al., 2010). In contrast, at the age of 14, dyscalculic subjects did not differ from TD adolescents in their ability to discriminate discrete and continuous magnitudes, supporting the notion that the non-symbolic magnitudes system might be intact at this age. In the context of the debate about the underlying mechanisms of DD, these results support the hypothesis that subjects with DD fail to link Arabic symbols to numerical values (Noel & Rousselle, 2011; Rubinsten & Henik, 2005). Future work should investigate the ability to process discrete and continuous magnitudes in younger children in order to understand if this system is functional or dysfunctional at an earlier point in development.

Despite the perpetual character of the deficits in number processing, the present results further reveal that the dyscalculic group showed larger improvements over the investigated time than the control group. At the same time, brain activity increased during development in the entire fronto-parietal numerical network. Together these results confirm that children with DD show behavioural (Geary et al., 2012; Landerl, 2013) and neuronal developmental changes in number processing. The improvements in brain activity allow a differentiated interpretation showing that domain-general as well as number-specific areas play a role in atypical development. Developmental changes were observed in the bilateral IPS, a region known to be crucial for number processing. It is worth pointing out, that in DD activation in the left IPS is observed only at the age of 14, but was not detectable 4 years earlier. This is in accord with the behavioural results and the finding that changes in the left IPS depend on the proficiency in number acuity (Emerson & Cantlon, 2014). Furthermore, in both conducted studies, dyscalculic adolescents elicited greater activation in the left frontal areas compared to TD peers. Together with the frontal activation increases during development, this points to the use of compensatory mechanisms and less effective task solving strategies. It can therefore be concluded, that children with DD undergo a development in number specific areas, but at the same time rely to a greater extent on domain-general regions revealing the probable use of compensation strategies.

Increased activation in parietal and fronto-temporal regions has also been reported in a study investigating the effects of learning arithmetic during one year (Rosenberg-Lee et al., 2011) and training of the mental number line led to remediation effects in parietal areas of children with DD (Kucian, Grond, et al., 2011). Similarly, these maturation effects were observed in our longitudinal study but also suggest a constrained development of number processing in DD. This is further substantiated by the observation that the fronto-parietal numerical network of dyscalculic children becomes more diffuse with increasing age. During development, activation patterns are expected to specialise and focus, reflecting the growing efficiency of the cognitive function (Durston et al., 2006; Karmiloff-Smith, 2010). Our results therefore suggest that the behavioural and neuronal development of number processing is delayed and inefficient in children with DD.

As outlined in the introduction, 7 to 10-year-old dyscalculic children show reduced white matter connections in the inferior and superior longitudinal fasciculi (Kucian et al., 2013; Rykhlevskaia et al., 2009). In typical development, the left hemispheric tracts are particularly suggested to be important for magnitude processing and arithmetic (Matejko & Ansari, 2015). This is further in agreement with study of Rosenberg-Lee et al. (2011), reporting an increased connectivity between the left frontal and parietal regions during one year. Therefore, the increase in left hemispheric activation in the IPS and the IFG pose the questions about a possible growth in connectivity and structural white matter changes during development. Answers to these questions can only be attained trough further investigation of the structural and functional longitudinal data.

In general, the present work confirms the stable deficits in number processing and arithmetic in DD. This should, however, not support the deterministic view that dyscalculic children do not show any development in numerical cognition. Quite on the contrary, our data disclose promising behavioural and neuronal improvements in number-specific areas. Results of the second study further reveal that adolescents show intact abilities to process various magnitudes. Yet, the increase in domain-general regions and the progression to a rather diffuse instead of a focussed number network corroborates the view of a delayed and inefficient developmental course. This leads to the conclusion that the deficiencies in DD do not vanish with time and should therefore be addressed with appropriated therapeutic measures.

4.3 Relationship of magnitude and space

The processing of numerosity and space is highly intertwined and difficult to disentangle - larger spatial dimensions usually mean more numerous and vice versa. Research of the last decades, however, mainly focused on the relationship of numbers and space, showing that numbers are spatially oriented and organised (e.g. Dehaene et al., 1993; Moyer & Landauer, 1967; Schweiter et al., 2005). This so-called mental number line is known to be deficient in subjects with DD (e.g. Landerl, 2013; Piazza et al., 2010), as was also observed in our subjects. In line with the literature, investigations conducted in the second study, revealed that adolescents with DD additionally showed deficits in visuo-spatial abilities (e.g. Kaufmann et al., 2009; Skagerlund & Träff, 2014). On closer inspection, difficulties were only found in more complex visuo-spatial abilities. In adolescents with DD, it therefore seems that the spatial-numerical representation is dysfunctional for symbolic numerical values, but intact for non-symbolic magnitude dimensions. In other words, simple spatial abilities are not affected in adolescents with DD and are consequently unlikely to contribute to the deficit in the mental number line. The further found differences in the complex visuo-spatial tasks might be explained by the involvement of higher order cognitive functions, which are known to be deficient in DD (see also Fias et al., 2013).

With respect to the neuronal mechanisms of space and number dimensions, a conjunction analysis revealed bilateral parietal activation. In addition, spatial processing elicited increased activation in the right IPS as compared to continuous and discrete magnitude processing. This might suggests that this area is involved in spatial processing. However, an important point to consider is, that besides being known as a key region for number processing, the IPS is reported to show activation in various tasks of spatial, motor, and attention functions (Hubbard, Piazza, Pinel, & Dehaene, 2005; Sack, 2009; Simon et al., 2004, 2002). Despite the enormous background of the literature it is yet to be revealed to which extent the IPS is involved and what its specific functions truly is. Single-cell experiments, however, reveal that in the IPS intermingled neurons encode either continuous, discrete, or both dimensions (Tudusciuc & Nieder, 2007, 2009). Together with the present findings, it may be suggested that the IPS incorporates several distinct but also overlapping spatial and numerical functions. There is need for future studies investigating tasks with numerical, spatial, motor and attentional content in the same population and find out more about the relationship of those functions in the intraparietal sulcus.

4.4 Outlook[3]

Despite the flourishing amount of studies in the field of neuroscience, the evidence based knowledge about development remains rather little. In a large number of studies, only certain age groups are investigated, leading to gaps of knowledge about development. As discussed previously, the contributions from studies with children and adults for the understanding of development are limited. A possible reason for this lack of evidence is that studying children and performing longitudinal studies is challenging and time-consuming. However, to fill these gaps and understand typical and, in particular, atypical development, studies with children at different ages are needed. Furthermore, cross-sectional longitudinal designs, combining the advantages of both methods while restricting the problems of longitudinal data collection, provide an alternative approach to study development. Studies investigating training effects and learning during, but also after, the acquisition of skills will further contribute to the whole picture of development.

The situation in the research field of numerical cognition and DD is similar. Apart from valuable knowledge about the heterogeneity and complexity of the deficits in DD, little is known about the origins and the development of this learning disability. As a result, facts about the interaction with environmental factors and implications for therapy are lacking. In a first attempt, the comparability and applicability of findings should be improved. Conformity in the diagnostic criteria for research would lead to better comparable evidence. Striving for homogeneity within groups, studies mainly include children without comorbid disorders. To meet the heterogeneity of the clinical picture, various groups of dyscalculic children ought to be included in future studies.

[3] This chapter is based on readings from Kucian and von Aster (2014) and "Neuroscience: implications for education and lifelong learning" (The Royal Society, 2011).

For the sake of research quality, those variables need to be well controlled. Alternatively, future study designs could integrate several subgroups of dyscalculic children to pursue this goal.

A second step towards a better understanding of DD would be to take a broader view on the functional and behavioural picture. Until now most of the studies focussed on the deficient numerical functions in the parietal lobe. However, further deficient functions, its interconnections and dependencies within the neuronal network of numeracy are important to understand and should be addressed in future work. In addition to the evidence from brain activity, studies investigating changes in structure and connectivity would provide insight into development of numerical cognition. Moreover, subject-specific trajectories of development and learning might be a valuable source to understand typical and dysfunctional developmental patterns. Multi-dimensional approaches further offer the possibility to merge the pieces of information obtained by various methods and understand more about the etiology and the developmental course of dyscalculia.

Finally, results from studies should lead to effective and practical implications for education and therapy. The transfer of knowledge to the clinic, however, poses various challenges for researchers. Interdisciplinary work is desirable and crucial for a broader understanding of DD, but difficulties arise in aligning the field specific conforms into a uniform language and research approach. At a first glance research results are not intuitively understood and sometimes seem contradictory. This might lead to misinterpretation and avoidance to implement the knowledge into education and therapy. In the future, the efforts to transfer knowledge from science into the clinics and vice versa should be supported to a much larger extent.

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Appendix A

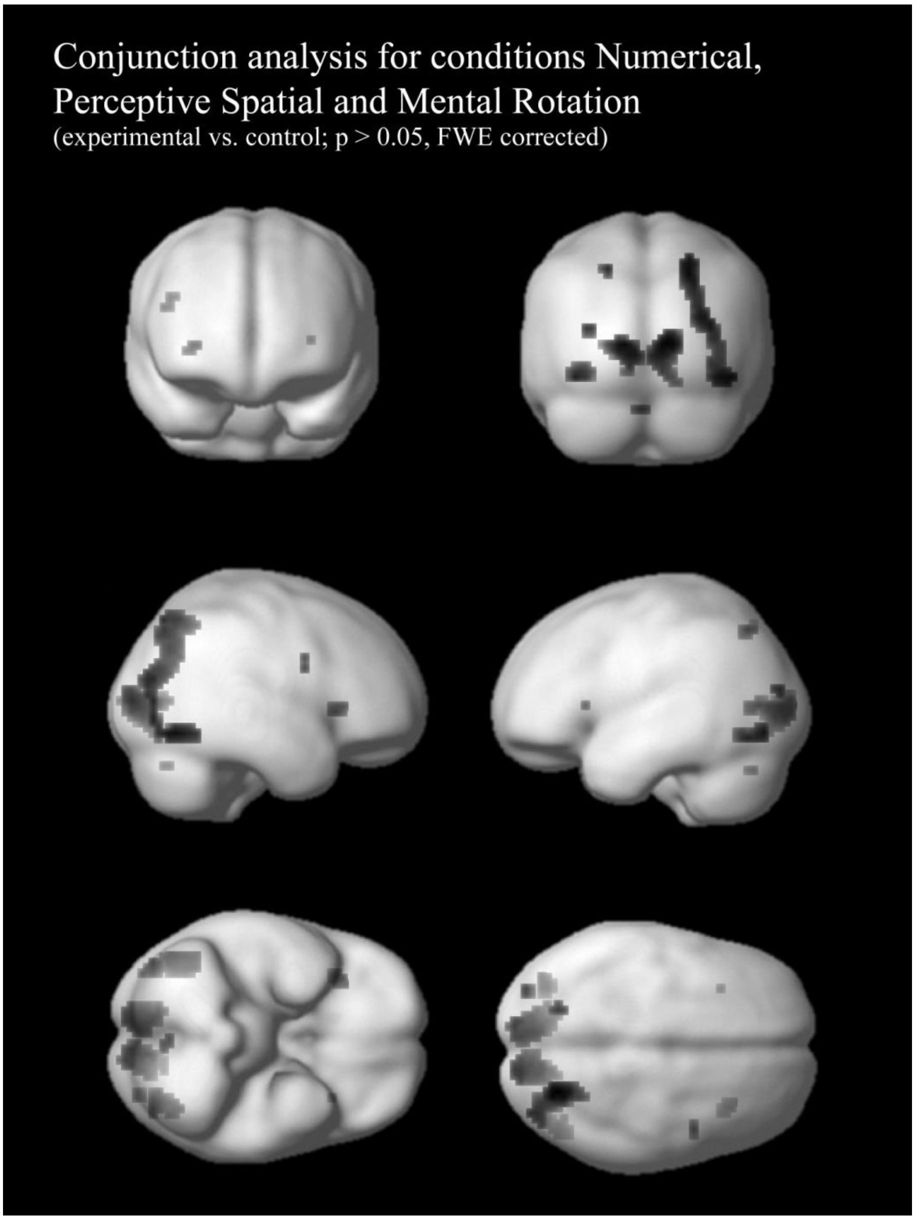
Regression Analysis

In order to investigate the developmental effects further, a regression analysis was performed with 16 data sets, comprised of both baseline and follow-up scans. The subjects' activation increase over time, for the contrast experimental minus control condition (interaction time point x condition), and arithmetic ability at the baseline assessment were included in the analysis.

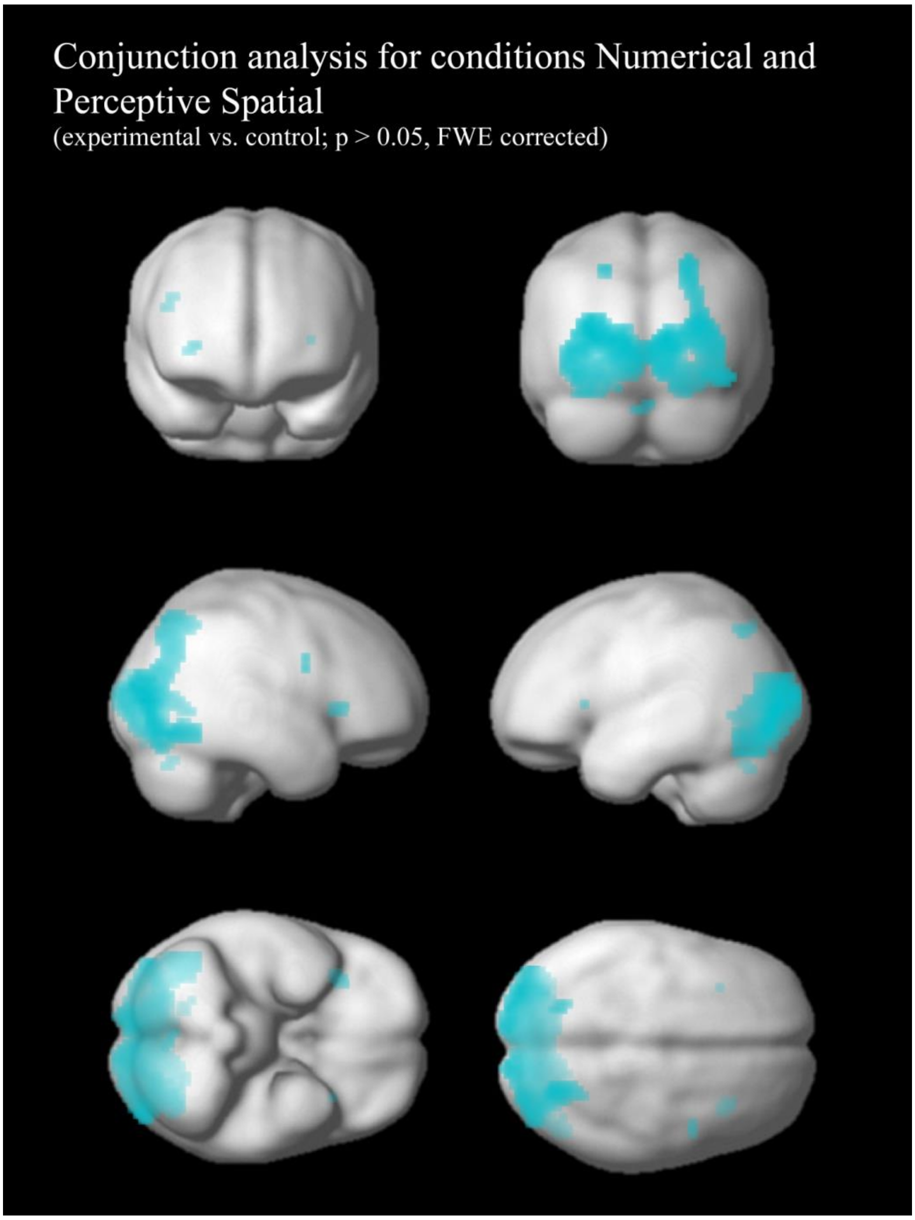
Results revealed a negative correlation between the activation increase over time and the number of correctly solved subtractions and additions at the baseline assessment (cluster-extent corrected $p < .001$). This indicates that children who solved fewer arithmetic problems correctly at baseline showed more activation increase over time in bilateral cingulate cortex extending into bilateral frontal gyri and supplementary motor area (SMA), bilateral insular lobe extending bilaterally into putamen and caudate nucleus, left middle occipital gyrus and right cerebellum. In the parietal lobe, broad activation increases were found in bilateral AG extending into inferior parietal lobe and IPS, and bilateral precuneus. There were no regions correlating positively with activation increase over time, meaning that a better behavioural performance does not result in more change over time.

Appendix B

Supplementary Figure 1



Supplementary Figure 2



Supplementary Figure 3